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Impact of low-dose computed tomography (LDCT) screening on lung cancer-related mortality (Review)

Bonney A, Malouf R, Marchal C, Manners D, Fong KM, Marshall HM, Irving LB, Manser R

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[Intervention Review]

Impact of low-dose computed tomography (LDCT) screening on lung cancer-related mortality

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ABSTRACT

Background

Lung cancer is the most common cause of cancer-related death in the world, however lung cancer screening has not been implemented in most countries at a population level. A previous Cochrane Review found limited evidence for the effectiveness of lung cancer screening with chest radiography (CXR) or sputum cytology in reducing lung cancer-related mortality, however there has been increasing evidence supporting screening with low-dose computed tomography (LDCT).

Objectives

To determine whether screening for lung cancer using LDCT of the chest reduces lung cancer-related mortality and to evaluate the possible harms of LDCT screening.

Search methods

We performed the search in collaboration with the Information Specialist of the Cochrane Lung Cancer Group and included the Cochrane Lung Cancer Group Trial Register, Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library, current issue), MEDLINE (accessed via PubMed) and Embase in our search. We also searched the clinical trial registries to identify unpublished and ongoing trials. We did not impose any restriction on language of publication. The search was performed up to 31 July 2021.

Selection criteria

Randomised controlled trials (RCTs) of lung cancer screening using LDCT and reporting mortality or harm outcomes.

Data collection and analysis

Two review authors were involved in independently assessing trials for eligibility, extraction of trial data and characteristics, and assessing risk of bias of the included trials using the Cochrane RoB 1 tool. We assessed the certainty of evidence using GRADE. Primary outcomes were lung cancer-related mortality and harms of screening. We performed a meta-analysis, where appropriate, for all outcomes using a random-effects model. We only included trials in the analysis of mortality outcomes if they had at least 5 years of follow-up. We reported risk ratios (RRs) and hazard ratios (HRs), with 95% confidence intervals (CIs) and used the I^2 statistic to investigate heterogeneity.

Main results

We included 11 trials in this review with a total of 94,445 participants. Trials were conducted in Europe and the USA in people aged 40 years or older, with most trials having an entry requirement of ≥ 20 pack-year smoking history (e.g. 1 pack of cigarettes/day for 20 years or 2 packs/day for 10 years etc.). One trial included male participants only. Eight trials were phase three RCTs, with two feasibility RCTs and one pilot RCT. Seven of the included trials had no screening as a comparison, and four trials had CXR screening as a comparator. Screening frequency included annual, biennial and incrementing intervals. The duration of screening ranged from 1 year to 10 years. Mortality follow-up was from 5 years to approximately 12 years.

None of the included trials were at low risk of bias across all domains. The certainty of evidence was moderate to low across different outcomes, as assessed by GRADE.

In the meta-analysis of trials assessing lung cancer-related mortality, we included eight trials (91,122 participants), and there was a reduction in mortality of 21% with LDCT screening compared to control groups of no screening or CXR screening (RR 0.79, 95% CI 0.72 to 0.87; 8 trials, 91,122 participants; moderate-certainty evidence). There were probably no differences in subgroups for analyses by control type, sex, geographical region, and nodule management algorithm. Females appeared to have a larger lung cancer-related mortality benefit compared to males with LDCT screening. There was also a reduction in all-cause mortality (including lung cancer-related) of 5% (RR 0.95, 95% CI 0.91 to 0.99; 8 trials, 91,107 participants; moderate-certainty evidence).

Invasive tests occurred more frequently in the LDCT group (RR 2.60, 95% CI 2.41 to 2.80; 3 trials, 60,003 participants; moderate-certainty evidence). However, analysis of 60-day postoperative mortality was not significant between groups (RR 0.68, 95% CI 0.24 to 1.94; 2 trials, 409 participants; moderate-certainty evidence).

False-positive results and recall rates were higher with LDCT screening compared to screening with CXR, however there was low-certainty evidence in the meta-analyses due to heterogeneity and risk of bias concerns. Estimated overdiagnosis with LDCT screening was 18%, however the 95% CI was 0 to 36% (risk difference (RD) 0.18, 95% CI -0.00 to 0.36; 5 trials, 28,656 participants; low-certainty evidence).

Four trials compared different aspects of health-related quality of life (HRQoL) using various measures. Anxiety was pooled from three trials, with participants in LDCT screening reporting lower anxiety scores than in the control group (standardised mean difference (SMD) -0.43, 95% CI -0.59 to -0.27; 3 trials, 8153 participants; low-certainty evidence).

There were insufficient data to comment on the impact of LDCT screening on smoking behaviour.

Authors' conclusions

The current evidence supports a reduction in lung cancer-related mortality with the use of LDCT for lung cancer screening in high-risk populations (those over the age of 40 with a significant smoking exposure). However, there are limited data on harms and further trials are required to determine participant selection and optimal frequency and duration of screening, with potential for significant overdiagnosis of lung cancer. Trials are ongoing for lung cancer screening in non-smokers.

PLAIN LANGUAGE SUMMARY

Impact of computed tomography (CT) on lung cancer screening

Background

Lung cancer is the most common cause of cancer-related death worldwide. Lung cancer survival is significantly dependent on when a person is diagnosed with the disease. It is essential to detect the disease as early as possible by radiography (chest x-ray) or by computed tomography (CT) scan, which is a more detailed type of radiography where multiple images of the lung are taken. The aim of this review was to gather information on the use of CT scan to detect lung cancer earlier and to find out if early detection of lung cancer reduces death from lung cancer. We also evaluated potential harms that can occur from using CT to screen for lung cancer, such as additional investigations and their related complications.

Description of included trials

The evidence is current to 31 July 2021. We included 11 trials, with a total of 94,445 participants. The trials came from the USA and Europe. The earliest trial started in 1991, and the most recent started in 2011. The participants were adults over the age of 40. The frequency of screening with CT ranged from yearly to more than 2.5 years.

Key findings

Eight of the trials (91,122 participants) were included in the main outcome analysis of lung cancer-related mortality. In people over 40 years with significant smoking exposure, CT screening reduced deaths from lung cancer by 21%, with 226 people needing to undergo screening to prevent one death from lung cancer. We also found that deaths from any cause (including lung cancer) were less with CT screening. However, the effect was much lower (only 5% reduction in risk). Lung cancer was detected more frequently in the group of people who had CT screening compared with no screening. However, CT scans can induce false-positive scans (a test that is positive or indeterminate for

lung cancer, when the person does not actually have lung cancer). We found that false-positive results were more common among people who were screened with CT than chest x-ray. Because of that, those that underwent CT screening had more tests to investigate both cancer and non-cancer-related diseases. Screening also implies a risk of detecting lung cancers that may have never progressed to cause harm to the person (this is referred to as overdiagnosis). The risk of lung cancer overdiagnosis with CT screening was estimated to be 18%.

The trials were too different or did not provide enough information to look at the impact of screening on stopping smoking or quality of life. There was some evidence to suggest there were no long-term psychological harms from screening, with some people in the CT screening group feeling less anxious compared to the control groups who were not offered screening.

Certainty of evidence

The overall certainty of evidence was moderate when it came to outcomes regarding death, with moderate- to low-certainty evidence for other outcomes. The certainty rating for outcomes reflects the authors' confidence and certainty in the outcome being correct.

Summary of findings 1. Low-dose computed tomography (LDCT) screening compared to no LDCT screening for lung cancer-related mortality

Low-dose computed tomography (LDCT) screening compared to no LDCT screening for lung cancer-related mortality

Patient or population: healthy adults
Setting: hospitals or screening centres
Intervention: LDCT screening
Comparison: no LDCT screening

Outcomes	№ of participants (trials) follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects*(95% CI)	
				Risk with no screening	Risk difference
Lung cancer-related mortality - planned time points Follow-up: 6 years to 10 years from randomisation	91,122 (8 RCTs)	⊕⊕⊕⊖ **Moderate**[a]	**RR 0.79** (0.72 to 0.87)	Trial population	
				21 per 1000	**4 fewer per 1000 people screened** (3 fewer to 6 fewer)
All-cause mortality - planned time points Follow-up: 6 years to 10 years from randomisation	91,107 (8 RCTs)	⊕⊕⊕⊖ **Moderate**[a]	**RR 0.95** (0.91 to 0.99)	Trial population	
				89 per 1000	**4 fewer per 1000 people screened** (1 fewer to 8 fewer)
Overdiagnosis Time point: ≥ 10 years from randomisation excluding CXR trials	28,656 (5 RCTs)	⊕⊕⊖⊖ **Low**[a,c]	**RD 0.18** (-0.00 to 0.36)	Trial population	
				180 more lung cancers overdiagnosed per 1000 lung cancers detected (0 more to 360 more)	
Number of invasive tests Time point: 3 years to 10 years from randomisation	60,003 (3 RCTs)	⊕⊕⊕⊖ **Moderate**[a]	**RR2.60** (2.41 to 2.80)	Trial population	
				31 per 1000	**49 more per 1000 people screened** (45 more to 55 more)
Any death postsurgery	409 (2 RCTs)	⊕⊕⊕⊖ **Moderate**[a]	**RR 0.68** (0.24 to 1.94)	Trial population	

Time point: 6 years to 9 years from randomisation				**48 per 1000**	**15 fewer per 1000 people screened** (37 fewer to 45 more)
Health-related quality of life - anxiety Time point: 10 months to 5 years from randomisation Measured by different scales	8153 (3 RCT)	⊕⊕⊖⊖ **Low**[a,b]	**SMD -0.43** (-0.59 to -0.27)	Trial population **SMD 0.43 lower** (0.27 to 0.59 lower)	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **CXR**: chest x-ray; **OR:** odds ratio; **RCT**: randomised controlled trial; **RR:** risk ratio; **RD:** risk difference**, SMD:** standardised mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level due to high risk of "other bias" in Becker 2020, De Koning 2020, Infante 2015, and Pastorino 2012.
[b]Downgraded one level due to indirectness: only a subset of the trial population were included for quality assessment.
[c]Downgraded one level due to heterogeneity.

BACKGROUND

Description of the condition

Lung cancer remains the most common cause of cancer-related death in the world (Ferlay 2019), resulting in an estimated 1.76 million deaths in 2018 (WHO 2018). Whilst historically a male predominant condition, the incidence of lung cancer is now comparable in men and women in the USA, representing approximately 13% of all new cancer diagnoses (Siegel 2019). In Germany, New Zealand, Denmark, Canada, the Netherlands and the USA, age-specific lung cancer incidence rates have declined in males with each 5-year birth cohort, with significant transition from male to female dominance in these countries in the younger age groups (30 to 49 years old) (Fidler-Benaoudia 2020). There is a concerning upward trend in lung cancer-related deaths in younger women (Levi 2007), with the death rate from lung cancer expected to exceed breast cancer-related deaths in Europe in women (Malvezzi 2017). The current 5-year survival for lung cancer is 19% in the USA, with poorer outcomes in small cell lung cancer and in the advanced stages (Howlader 2020). In the last decade, prognosis has improved in stage III and IV non-small cell lung cancer (NSCLC) with the introduction of immunotherapy and targeted molecular therapy (Howlader 2020; NICE 2019). However, these treatments are mostly not considered curative, with the 5-year survival in the USA for metastatic NSCLC being 6%, compared to 61% for local NSCLC (Howlader 2020). Complete resection of early-stage NSCLC has the greatest potential for long-term survival (beyond 10 years) (Hubbard 2012).

Tobacco smoking is recognised as the most significant risk factor for lung cancer (Halpern 1993; Peto 1994), and as such, primary prevention is an essential component of public health campaigns. However, additional factors such as age, genetic factors, airway obstruction, infections and environmental exposure affect risk (Alberg 2007; Bach 2003), with exposure to ambient air pollution increasingly contributing to the global burden of lung cancer (WHO 2016). Particularly in females, adenocarcinomas with detectable molecular mutation are more common in never-smokers compared to people with a tobacco-exposure history (Subramanian 2007). A number of validated risk prediction tools have been developed which incorporate smoking history, in addition to other risk factors, to estimate lung cancer risk (Cassidy 2008; Tammemägi 2013). These risk prediction models have been suggested to improve participant selection for lung cancer screening and have already been incorporated into screening programmes (Field 2019; ten Haaf 2017).

Description of the intervention

Lung cancers are commonly diagnosed at an advanced stage, with 48% of patients in Australia and 61% of patients in Denmark having metastatic NSCLC at the time of diagnosis (Walters 2013). Hence, several trials have evaluated the role of screening for the detection of preclinical disease. Early lung cancers may be visible on plain chest radiography (CXR) or computed tomography (CT) as a pulmonary nodule. A lung nodule is defined as a focal opacity, more or less well defined, measuring up to 3 cm (Hansell 2008). The sensitivity of CXR for the detection of pulmonary nodules < 1 cm is poor (Quekel 1999). Furthermore, in people presenting with symptoms of lung cancer, the sensitivity of CXR is only 80% or less (Bradley 2019). A CT scan is a more detailed type of radiography imaging which uses a rotation x-ray source. Multiple x-ray attenuation measurements are taken from different angles and then processed on a computer using reconstruction algorithms to produce cross-sectional images or virtual slices of a body. These cross-sectional images are able to detect pulmonary nodules < 1 cm more reliably than CXR due to improved resolution and reduced obscuration from overlapping mediastinal, cardiac and chest wall structures. This is beneficial in the detection of small early-stage lung cancers, however CT-detected nodules are not specific to cancer, with differentials including benign nodules, such as hamartomas, granulomas, and inflammatory nodules. Additional incidental findings described with low-dose computed tomography (LDCT) include mediastinal lymphadenopathy, coronary artery calcification, aortic aneurysm, and non-pulmonary malignancies (Swensen 2002).

How the intervention might work

LDCT screening has been established as a more sensitive tool to detect lung cancer at an early and resectable stage compared with CXR (Diederich 2002; Nawa 2002; Sobue 2002; Sone 2001; Swensen 2002). An earlier Cochrane Review on lung cancer screening found that annual CXR did not significantly reduce lung cancer mortality (Manser 2013). The same review concluded that LDCT screening was associated with a reduction in lung cancer mortality compared with CXR among high-risk former and current smokers. Reviewers for the 2013 US Preventive Services Task Force Evidence Synthesis also concluded that high-certainty evidence shows that LDCT screening can significantly reduce mortality from lung cancer (Humphrey 2013). The findings of both of these systematic reviews were based largely on the results of the National Lung Screening Trial (NLST, Aberle 2011) which used the comparator of CXR in a group of high-risk former and current smokers. In a more recent systematic review, conducted as part of a Health Technology Assessment for the National Institute for Health Research (NIHR) in the UK, the reviewers concluded that LDCT may be clinically effective in reducing lung cancer mortality, but there is considerable uncertainty (Snowsill 2018).

Why it is important to do this review

Despite multiple international guidelines recommending LDCT screening for high-risk former and current smokers, and calls for the implementation of screening, to our knowledge a nationally co-ordinated screening programme has not been broadly adopted, apart from in Korea (Lewin 2016; Moyer 2014; Oudkerk 2017; Zhou 2015). In the USA, the Center for Medicare and Medicaid Services has approved coverage and reimbursement for lung cancer screening for individuals who meet certain criteria (Jensen 2015). However, in the absence of a co-ordinated programme, there have been concerns about the low up take of screening and considerable variability in false-positive rates between different providers (Pinsky 2018).

There was an urgent need for a contemporary systematic evidence synthesis that incorporates the growing evidence base from RCTs on both benefits and harms of screening in order to better understand the potential magnitude of any benefit and to understand in which groups any benefits might outweigh the harms. False-positive test results and overdiagnosis are both potential sources of harm from screening which may lead to unnecessary interventions with adverse psychological impacts, morbidity and mortality. Overdiagnosis refers to the detection and diagnosis of lung cancers by screening which would have never

caused the person harm, such as death or symptoms, in their lifetime when left untreated (Brodersen 2018). In a recent review of RCTs in which LDCT was compared to usual care (no screening), it was estimated that 49% of lung cancers detected by screening may have been overdiagnosed (Brodersen 2020). Radiation exposure has similarly been considered, with Gierada et al. describing an estimated risk of radiation-induced cancer mortality after 20 annual chest LDCTs of 0.1%, based on a linear no threshold model of ionising radiation effects (Berrington de González 2008; FDA 2017; Gierada 2020; Rampinelli 2017). In the UK, screening for lung cancer is part of the National Health Service (NHS) long-term plan, and its ambition is to reach around 600,000 people over 4 years, detecting approximately 3400 cancers across the UK (NHS 2019).

The purpose of this review was to assess the evidence regarding LDCT screening methods to reduce lung cancer-related mortality and to evaluate the possible harms associated with screening. Additionally, we estimated the incidence of lung cancer and impact on smoking behaviour following screening. Another reason for conducting this review was to involve consumer participation to allow for different perspectives on outcomes and to disseminate the review findings.

OBJECTIVES

To determine whether screening for lung cancer using LDCT of the chest reduces lung cancer-related mortality and to evaluate the possible harms of LDCT screening.

METHODS

Criteria for considering studies for this review

Types of studies

We considered randomised controlled trials (RCTs). Randomisation by groups, clusters or individuals was acceptable. All trials reporting mortality as an outcome were eligible for inclusion in the review; however, we did not include those with < 5 years of mortality follow-up data in quantitative synthesis.

We excluded:

- observational cohort studies; and
- case-series studies.

Types of participants

We included trials with asymptomatic adults from all backgrounds. We excluded trials in adults with previous diagnosis and treatment of lung cancer. We verified entry requirements for all included trials to include only preclinical nodules.

Types of interventions

- Intervention
  - LDCT, defined as a volumetric CT dose index of ≤ 3 mGy in a standard sized patient (height 170 cm, weight 70 kg) in 2016 (Kazerooni 2016). Newer technological improvements (iterative reconstruction) have enabled further dose reductions (Willemink 2013).
- Comparator
  - LDCT screening versus no screening
  - LDCT screening versus any non-LDCT intervention, including (but not limited to) CXR, sputum cytology or biomarkers (alone or in any combination)

In addition, we included trials which compared different frequencies of screening with LDCT, such as annual LDCT versus biennial LDCT.

Types of outcome measures

Primary outcomes

- Lung cancer-related mortality ≥ 5 years post-randomisation
- Harms of screening at any time point, including the number of invasive tests performed in those with a false-positive diagnosis (positive screen in the absence of lung cancer), and any complications arising from these tests, including death

Secondary outcomes

- All-cause mortality (death from any cause, including lung cancer)
- Lung cancer incidence (during screening and postscreening period in those trials which have recorded the incidence postscreening, to capture data on overdiagnosis where possible). In this review, baseline screen incidence data included both incident and prevalence cases of lung cancer first detected during baseline screening.
- False-positive rates and recall rates (proportion of participants recalled for interval CT at 3 months and > 6 months for follow-up of a nodule or suspected lung cancer)
- Impact on smoking behaviour: cessation, relapse rates, smoking intensity
- Health-related quality of life (HRQoL)/psychosocial consequences. We considered all time points recorded in trials, with an analytic plan for 6 months, 12 months, and 24 months interval assessments.

We recorded, where possible, any other outcomes presented in the primary studies, including but not limited to, stage at diagnosis, histology, radiation exposure, use of biomarkers, response rate, adherence to screening, contamination, interval lung cancers, false negatives, cost, medication implications, and incidental findings.

Search methods for identification of studies

Electronic searches

We searched the following electronic databases from inception to 31 July 2021. We performed the search in collaboration with the Information Specialist of the Cochrane Lung Cancer Group.

- Cochrane Lung Cancer Group Trial Register
- Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library, current issue) (Appendix 1)
- MEDLINE, accessed via PubMed (Appendix 2)
- Embase (Appendix 3)

We performed the MEDLINE search using the Cochrane highly sensitive search strategy, sensitivity and precision-maximising version (2008 version) as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022).

We also conducted searches in the following clinical trials registries to identify unpublished and ongoing trials.

- ClinicalTrials.gov
- WHO International Clinical Trials Registry Platform (ICTRP)

We applied no restriction on language of publication.

Searching other resources

Ongoing trials and grey literature

We used the following additional resources.

- Abstracts from 2018 and onwards from international lung cancer meetings, including World Conference on Lung Cancer, American Thoracic Society Conference, European Respiratory Society Conference, American Society of Clinical Oncology (ASCO) Conference, European Society of Medical Oncology (ESMO) Conference and European Conference of Clinical Oncology (ECCO)
- We searched the bibliographies of identified trials and narrative reviews for additional citations.
- We contacted authors of primary studies and experts in the field of lung cancer screening to determine whether they were aware of any additional relevant unpublished or published studies or works in progress.

We applied no restriction on language of publication.

Data collection and analysis

Selection of studies

We selected trials for inclusion according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022).

Two review authors (AB and CM) using Covidence (Covidence 2017) independently screened all titles and abstracts retrieved by electronic searches. Two review authors (AB and DM) then obtained the full texts for all relevant trials and independently checked the eligibility of each trial against review eligibility criteria. We pursued discordant evaluations by discussion to reach consensus. When necessary, we involved a third review author (RManser). We report the results of the trial selection process using a PRISMA flow diagram (Moher 2009).

Data extraction and management

The review authors developed a data extraction form using Covidence (Covidence 2017). Two review authors (AB and RM) independently extracted relevant data and performed a cross-check. To reach consensus, we involved a third review author when necessary (RManser or DM). We were not blinded to the names of trial authors nor to the institutions where trials were conducted and funded. When we encountered multiple publications for the same trial, we chose the first publication dealing with the primary endpoint in this review as a study identifier (study ID).

We collected the following data.

- Source: citation, trial name if applicable and contact details
- Eligibility criteria and reasons for exclusion
- Methods: trial design, total duration of trial, number of trial centres and locations, trial setting, date of trial and dates of first and last included participants
- Characteristics of participants: number of participants, participant characteristics (age, sex, smoking status, performance status), country, ethnicity
- Characteristics of interventions (e.g. frequency of scanning, dose of CT, duration of screening, interpretation of scans, criteria for significance)
- Outcomes: primary and secondary outcomes (with definitions) and time points
- Results: number of participants allocated to each group, and for each outcome of interest, sample size, missing participants, summary data for each group, estimate of effect with confidence interval and P value and subgroup analyses
- Miscellaneous: funding source, notable conflicts of interest of trial authors

Assessment of risk of bias in included studies

Two review authors (AB and RM) independently applied the Cochrane RoB 1 tool in order to assess quality and potential biases across included trials (Higgins 2017). We rated each domain of the tool as having 'low', 'high', or 'unclear' risk of bias at trial level and for each outcome if possible, and we supported the rating of each domain with a brief description. We summarised risk of bias for each outcome within a trial by considering all domains relevant to the outcome (i.e. both trial-level entries, such as allocation sequence concealment, and outcome-specific entries, such as blinding). We provided a figure to summarise the risk of bias.

If the two review authors did not reach consensus, a third review author (RManser or DM) was consulted.

Using the Cochrane RoB 1 tool, we considered the following domains.

- Selection bias - generation of allocation sequence: we scored 'low risk' when a random component in the sequence generation process was stated, 'high risk' when a non-random method was used such as date of birth or hospital admission and 'unclear risk' if not specified in the paper.
- Selection bias - allocation concealment (selection bias): we scored 'low risk' when the allocation to intervention methods were reported such as using some form of centralised randomisation scheme, an on-site computer system or sealed opaque envelopes, we scored 'high risk' when the allocation concealment method was not appropriate and 'unclear risk' when the method was not specified in the paper.
- Performance bias - blinding of participants and personnel: we scored 'low risk' when the blinding of participants and key trial personnel was ensured. We scored 'high risk' when there was no blinding or incomplete blinding, for the review outcome was likely to be influenced by lack of blinding such as smoking behaviour changes. We scored 'unclear' when there was insufficient information to make this judgement.
- Detection bias - blinding of outcome assessors: we scored 'low risk' when the outcome assessment was blindly performed. We scored 'high risk' when there was no blinding of the other review outcome assessment. We scored 'unclear' when there was insufficient information to make this judgement.

- Attrition bias - incomplete outcome data: we scored 'low risk' when there were no missing data, reasons for missing data were provided, the number of missing data were balanced across the groups or when appropriate method was used to impute missing data. We scored 'high risk' when there was > 20% missing data or imbalance in numbers or reasons for missing data across the trial groups. We scored 'unclear risk' when there was insufficient information to make this judgement.
- Reporting bias - selective reporting: we scored 'low risk' when the trial protocol was available and all prespecified trial outcomes were reported. Moreover, when the protocol was not available, and it was clear from the published papers that all expected outcomes are reported, these trials were still rated at low risk. We scored 'high risk' when not all prespecified outcomes were reported, reported outcomes on subsets of the data, and incomplete reporting of the outcomes. We scored 'unclear risk' when there was insufficient information to make this judgement.
- Other sources of bias - other bias: we scored 'low risk' if the trial appeared to be free of other sources of bias. We scored 'high risk' when there was at least one important bias, for example, the risk of contamination between the intervention and the control groups.

For cluster-RCTs we addressed the following additional issues (Higgins 2022).

- Randomisation process: we reported on the number of clusters involved and whether randomisation was performed at a single time point or in batches.
- Recrutment bias: we investigated bias relevant to whether the participants within the cluster were aware of the intervention, the timing of randomisation and recruitment of individuals in addition to any baseline imbalance between individuals, not clusters.
- Bias due to deviations from intended interventions: we dealt with this issue similar to the individually-randomised trials.
- Bias due to missing outcome data: we reported missing data for both the participants and the cluster.
- Bias in measurement of the outcome: we reported on this bias in the same way as to the individually-randomised trials.
- Other bias: we reported on this bias the same way as the individually-randomised trials.

Measures of treatment effect

For time-to-event outcomes (overall survival and relapse-free survival), we had planned to use hazard ratios (HRs) to measure intervention effects after validating the proportional hazards assumption, so far as possible. However, only a few trials reported the hazard of death from the time of the enrolment point and reported each HR along with the 95% confidence Interval (CI).

For dichotomous outcomes (i.e. lung cancer cases detected by CT screening), we used the extracted data from the original trials for both screened and unscreened controlled groups to estimate the overall incidence of newly-diagnosed lung cancer cases.

We also calculated the risk of overdiagnosis by estimating the risk ratio (RR) of lung cancer (with 95% CIs) in the screened group compared with the control group in trials which have reported the cumulative incidence of lung cancer post the active phase of screening. The primary analysis for overdiagnosis was limited to trials in which the control group did not have any active screening; however we also estimated the risk of overdiagnosis from CT screening relative to that of CXR screening in those trials where the control group were offered CXR screening in a separate analysis.

For continuous outcomes (HRQoL), we used mean differences (MDs) between treatment arms when a similar scale was implemented to measure outcomes, and standardised mean differences (SMDs) when different scales were used to measure the same outcome. This was applied when anxiety data were pooled across the four trials reported on anxiety. If we confirmed that higher scores for continuous outcomes have the same meaning for the particular outcome, we explained the direction, and reported if directions were reversed. We analysed data on an intention-to-screen basis.

Unit of analysis issues

For the included RCTs, the individuals were the unit of analysis by practice.

For cluster-RCTs we identified trials using a cluster randomisation as a way of avoiding contamination bias. Randomisation might have been performed by hospitals, centres and cities. When including data from these trials into meta-analyses we used the effective sample size method as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022). We calculated the effective sample size of groups in each cluster trial to be the original sample size divided by the 'design effect'. We calculated the cluster design effect by 1+ (M -1) ICC, where M represented the average cluster size and ICC was the interclass correlation coefficient. For dichotomous data, we divided both the total number of participants and the number experiencing the event by the same design effect. For continuous data, only the sample size was reduced and the means and standard deviations (SDs) stayed the same (Higgins 2022).

Trials with multiple treatment groups

For trials with multiple comparison groups that compared two or more intervention groups with the same control group, we first tried to combine groups to create a single pair-wise comparison. We calculated within-study correlation as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022).

Dealing with missing data

When data were missing or unsuitable for analysis, we (DM) contacted trial authors to request further information using email addresses from trial reports, from trial registers or from trial author institutions. When data were missing to the extent that the trial could not be included in the meta-analysis and attempts to retrieve data had been exhaustive, we presented the results in the review and discussed them in the context of trial findings. For each trial, we checked whether intention-to-screen analysis was applied (i.e. the number of analysed participants equalled the number of randomly-assigned participants).

Assessment of heterogeneity

We followed Cochrane recommendations for assessment of heterogeneity (Higgins 2022). We visually investigated heterogeneity by using forest plots generated via Review Manager

5 (RevMan 5) (Review Manager 2020). We assessed statistical heterogeneity of treatment effects between pooled trials for each considered outcome by using the I^2 statistic to quantify the degree of heterogeneity (Higgins 2002), and we considered I^2 > 30% as showing moderate heterogeneity, with I^2 > 75% signifying substantial heterogeneity.

Assessment of reporting biases

We were unable to generate funnel plots and performed Egger's linear regression tests in order to investigate reporting biases for any of the outcomes, as the maximum number of trials included in a single meta-analysis was insufficient (9, with at least 10 trials required). We followed recommendations provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022). We noted interpretation was difficult when small numbers of trials (< 10) were included. When we observed evidence of small-study effects, we performed sensitivity analyses according to regression-based adjustment methods.

Data synthesis

We used intention-to-screen analyses by including all randomised people who were invited to screening where possible, and have specified when intention-to-screen analysis was not used for a study. When there were repeated observations on participants in long-term trials, we included outcomes at different time points in separate analyses. We combined data when outcomes from different trials were measured at similar time points.

If sufficient clinically-similar trials were available, we performed meta-analyses, applying both fixed- and random-effects meta-analyses according to recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022). We entered data into RevMan 5 (Review Manager 2020). A review author (RM) entered the data, and a second review author (AB) double-checked the data for accuracy. We only included trials in the meta-analysis for lung cancer-specific mortality and all-cause mortality if they had at least 5 years of follow-up. We applied the generic inverse-variance method and random-effect models for all type of outcomes. For dichotomous outcomes, we applied the DerSimonian and Laird method (DerSimonian 1986).

For calculating overdiagnosis data we used the following formula for the diagnosis rate in the screened group and then bootstrapped this to obtain 95% normal based CIs.

[(Lung cancer incidence in LDCT screening group/total number of participants in screening group) - (lung cancer incidence in control group/total number of participants in control group)] / (lung cancer incidence in LDCT screening group/total number of participants in screening group)]

Subgroup analysis and investigation of heterogeneity

We investigated the level of heterogeneity. When data were heterogenous we checked and identified the sources of this heterogeneity. When heterogeneity remained considerably high I^2 > 75%, we reported the results narratively with no meta-analyses.

- We performed a number of subgroup analyses:
  - age
  - sex
  - smoking history or validated measures of lung cancer risk (including risk prediction model)
  - screening interval
  - geographical region
  - by control types - usual care or CXR

Sensitivity analysis

We conducted sensitivity analyses to assess whether results were robust to assess decisions made during the review process such as our assessments about clinical heterogeneity. We looked at the impact of types of control groups. If we identified sufficient trials, we restricted the analysis to trials at low risk of bias, based on overall risk of bias judgement (Higgins 2017).

Summary of findings and assessment of the certainty of the evidence

As suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022), we presented a summary of findings table, reporting the following outcomes listed in order of priority.

- Lung cancer-related mortality, using planned follow-up time points (predefined by trial as opposed to unplanned, post hoc, extended follow-up)
- All-cause mortality, using planned follow-up time points
- Overdiagnosis (this replaced lung cancer incidence)
- Number of invasive tests (to represent harms of screening)
- Any death postsurgery (this replaced the impact on smoking behaviour with an additional harm of screening outcome)
- Anxiety (to represent HRQoL and psychosocial consequences)

We followed the GRADE approach when creating our summary of findings table, as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022). The GRADE approach specifies four levels of certainty (high, moderate, low, or very low) to rate the certainty of evidence in the following domains.

- Risk of bias
- Inconsistency
- Indirectness
- Imprecision
- Publication bias

RESULTS

Description of studies

Results of the search

Overall, we identified 5390 citations during our electronic search, of which we selected 43 for full-text review. The evidence is current to 31 July 2021. Following full-text review, we included 11 trials (reported in 182 multiple citations). We excluded 30 citations, with additional details provided in Characteristics of excluded studies. We identified an additional 47 citations for the included trials during full-text review via searching of bibliographies and additional MEDLINE author searches. We identified two RCTs that were in keeping with our review protocol, that had not published mortality or harm data (Sagawa 2012; Yang 2018). The first is a Japanese trial that started in 2010, comparing LDCT and CXR over a 10-year period in people with a smoking history < 30 pack years

(e.g. < 1 pack of cigarettes/day for 30 years or < 1.5 packs/day for 15 years etc.) (Sagawa 2012). The second trial (Yang 2018), based in China, similarly includes participants who also do not have a strong smoking history, however participants must have at least one high-risk factor (family history of cancer or personal history of cancer, occupational exposures to carcinogenic agents, passive or active smoking exposure, or long-term exposure to cooking oils). This trial compares three rounds of biennial LDCT with no screening and started in 2013. These trials are described in more detail in Characteristics of ongoing studies.

The included trials were the US National Lung Screening Trial (NLST, Aberle 2011), German Lung Cancer Screening Intervention (LUSI, Becker 2020), French DEPISCAN trial (Blanchon 2007), Dutch-Belgian Nederlands-Leuvens Longkanker Screenings Onderzoek trial (NELSON, De Koning 2020), UK Lung Cancer Screening trial (UKLS, Field 2021), US Lung Screening Study (LSS, Gohagan 2005), Italian Detection And screening of early lung cancer by Novel imaging TEchnology trial (DANTE, Infante 2015), North American Jewish Hospital Lung Cancer Screening and Early Detection Study (LaRocca 2002), Italian Lung Cancer Screening trial (ITALUNG, Paci 2017), Multicentric Italian Lung Detection trial (MILD, Pastorino 2012), and the Danish Lung Cancer Screening Trial (DLCST, Wille 2016).

Search results are described in Figure 1.

Figure 1. Study selection flow diagram.

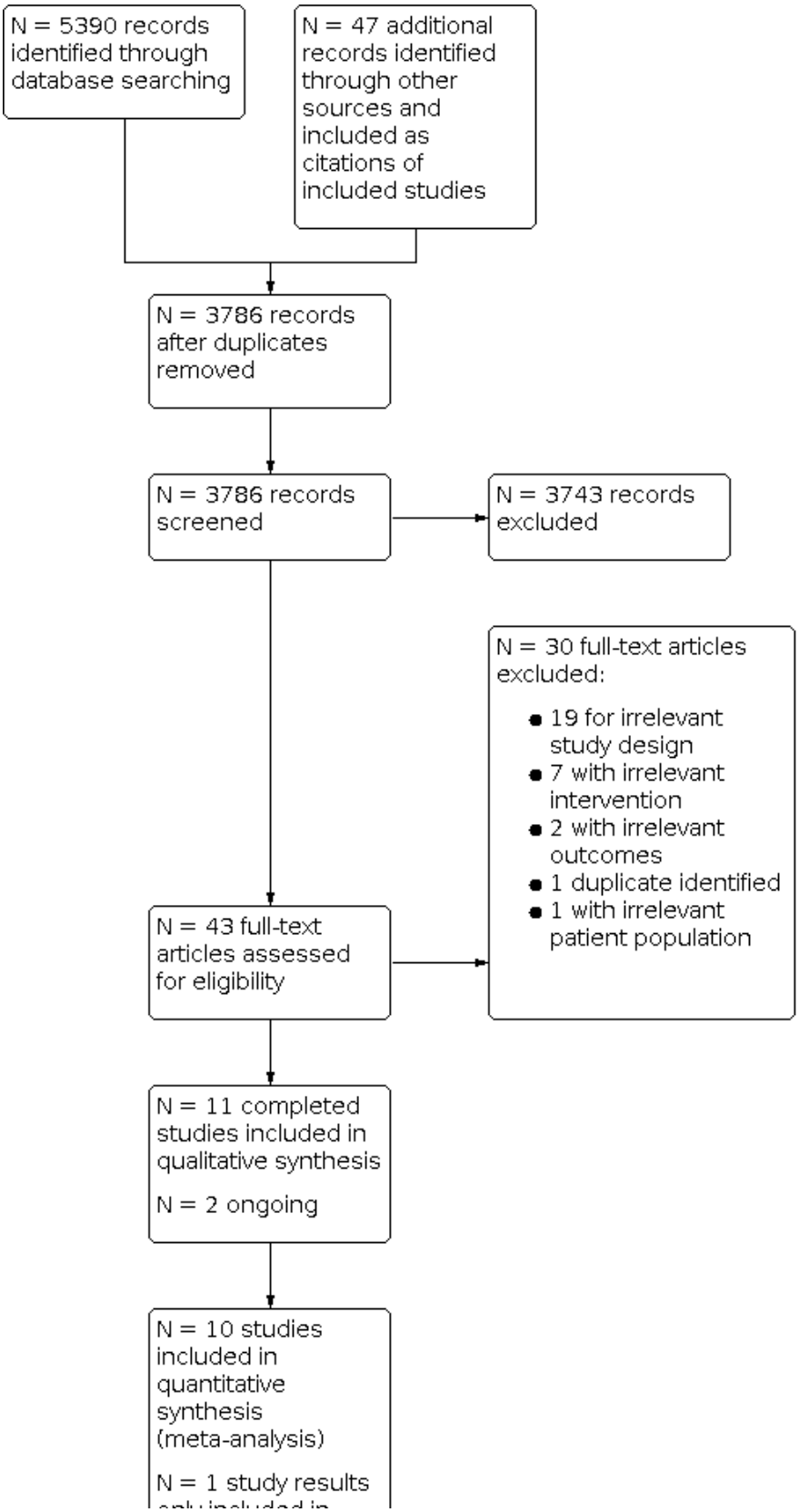
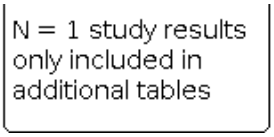


Figure 1. (Continued)



Included studies

Trial design and setting

Eight of the 11 trials were phase 3 RCTs (Aberle 2011; Becker 2020; De Koning 2020; Infante 2015; LaRocca 2002; Paci 2017; Pastorino 2012; Wille 2016), whilst the LSS (Gohagan 2005) and DEPISCAN (Blanchon 2007) trials were feasibility RCTs, and UKLS was a pilot RCT (Field 2021). Three of the 11 trials were conducted in the USA (Aberle 2011; Gohagan 2005; LaRocca 2002); the remaining trials were based in Europe.

All trials were conducted via hospitals or screening centres, with the number of sites varying from 1 to 33. The NLST had the most trial sites (Aberle 2011), followed by the French DEPISCAN trial with 14 sites (Blanchon 2007).

LaRocca 2002 was the earliest trial to start, in 1991, followed by Gohagan 2005 in 2000. Wille 2016 had the latest start date (2011) of the included trials, with the remaining trials starting between 2001 and 2007.

Trial participants

Overall 94,445 people were included across the trials. The NLST had the largest sample size of the included trials with 53,456 participants (Aberle 2011). The next biggest was the NELSON trial with 15,792 (De Koning 2020). Four trials had just over 4000 participants each (Becker 2020; Field 2021; Pastorino 2012; Wille 2016), whilst LSS (Gohagan 2005) and ITALUNG (Paci 2017) had over 3000 participants each. The DANTE trial had 2450 participants (Infante 2015). DEPISCAN had the smallest reported sample size of 765 participants randomised (Blanchon 2007), and with only 621 participants continuing after 144 withdrew consent. LaRocca 2002 reported 871 participants were randomised, however did not include allocation of participants.

In the UKLS trial (Field 2021), the number of participants included in Characteristics of included studies and number of participants in some analyses differ, as 87 participants in the UKLS trial were excluded post-randomisation from analysis of long-term data.

Inclusion criteria

Inclusion and exclusion criteria between the trials were similar, with trials having an overlapping age range from 40 years and above. Nine of the 11 trials had a lower age limit of 50 years or above (Aberle 2011; Becker 2020; Blanchon 2007; De Koning 2020; Field 2021; Gohagan 2005; Infante 2015; Paci 2017; Wille 2016). Ten of the 11 trials had an upper age limit of 75 years or less (Aberle 2011; Becker 2020; Blanchon 2007; De Koning 2020; Field 2021; Gohagan 2005; Infante 2015; LaRocca 2002; Paci 2017; Wille 2016). All trials, except UKLS (Field 2021), had a strong smoking history requirement as part of the inclusion criteria (at least 20 pack years or more). Field 2021 was one of the few trials to use a risk prediction model; with participants requiring a 5% risk of developing lung cancer in 5 years, based on the Liverpool Lung Project (LLP) Risk Prediction Model version 2 (LLPv2). The LLPv2 is a lung cancer risk calculator that incorporates factors such as age, tobacco smoking history, personal history of pulmonary disease or cancer, family history of lung cancer and occupational exposures (Field 2016).

Of note, the DANTE trial excluded all women from the trial (Infante 2015), and the NELSON trial (De Koning 2020) only recruited women in the Belgium arm of the trial, and not for the Netherlands cohort. No included trial reported equal representation of male and female participants.

In LaRocca 2002, participants required a normal or stable CXR prior to randomisation. The DANTE trial also required a baseline CXR and sputum cytology with clinical examination in both arms of their trial (Infante 2015).

In addition to the basic demographics provided in the Characteristics of included studies, the NLST included information about education status (Aberle 2011), with 32% of participants having a college degree or higher level of education. Only 48% of their cohort were current smokers. Weight data was also collected, with 1% of their cohort underweight, 28% normal weight, 43% overweight and 28% obese. In the UKLS trial (Field 2021), 46% of the cohort had an education up to or equal to secondary level and 54% beyond secondary school. The DLCST participants had a relatively even distribution of low, middle, and high socioeconomic status (Wille 2016), with 74% of the cohort having 10 years or less of schooling.

Intervention

All trials used chest LDCT as their primary intervention, with reported settings ranging from 90 kVP to 140 kVP and 20 mA to 60 mA. The frequency and duration of LDCT varied between trials, with annual LDCT occurring in nine of the 11 trials (Aberle 2011; Becker 2020; Blanchon 2007; Gohagan 2005; Infante 2015; LaRocca 2002; Paci 2017; Pastorino 2012; Wille 2016). In the UKLS trial (Field 2021), only one LDCT was performed during the trial. The LSS trial conducted annual screening over 2 years (Gohagan 2005), whilst DEPISCAN (Blanchon 2007) and NLST (Aberle 2011) performed annual LDCT for 3 years. The ITALUNG trial performed annual LDCT for 4 years (Paci 2017), whilst four of the 11 trials performed annual LDCT screening for 5 years (Becker 2020; Infante 2015; LaRocca 2002; Wille 2016). The MILD trial had two intervention arms (Pastorino 2012), one for biennial scans and one for annual scans; over the 10-year screening period, the biennial arm had a median of four LDCT scans whilst the annual group had a median of seven LDCT scans. The NELSON trial used incrementing intervals for the LDCT (De Koning 2020), with a baseline scan, then at 1 year, 2 years, and 2.5-year intervals.

The majority of the trials used no screening for the control arm (Becker 2020; De Koning 2020; Field 2021; Infante 2015; Paci 2017; Pastorino 2012; Wille 2016), however four of the 11 trials used annual CXR in the comparison arm for the duration of the screening period (Aberle 2011; Blanchon 2007; Gohagan 2005; LaRocca 2002).

Six of the 11 trials used diameter criteria and no volumetric assessment using computer-assisted tools to determine significance of pulmonary nodules (Aberle 2011; Blanchon 2007; Gohagan 2005; Infante 2015; LaRocca 2002; Paci 2017). LUSI (Becker 2020), UKLS (Field 2021), and DLCST (Wille 2016) used both diameter and volumetric criteria to determine nodule significance. The NELSON trial (De Koning 2020) and MILD trial (Pastorino 2012) used volumetric analysis only, for evaluating nodules at baseline and calculating at 3-month follow-up the volume doubling time of nodules.

Outcomes and follow-up

Of the published data, follow-up ranged from 5 to 12 years post-randomisation (Aberle 2011; Becker 2020; De Koning 2020; Field 2021; Gohagan 2005; Infante 2015; Paci 2017; Pastorino 2012; Wille 2016). NLST (Aberle 2011), NELSON (De Koning 2020), ITALUNG (Paci 2017), and MILD (Pastorino 2012) all have median follow-ups of 10 or more years. The DANTE (Infante 2015) and MILD (Pastorino 2012) trials both published mortality data before and beyond 5 years, with only the later time points included. Yang 2018 published 2-year mortality data following the baseline scan, however this trial is ongoing.

Eight of the 11 trials used prespecified nodule follow-up (Becker 2020; Blanchon 2007; De Koning 2020; Field 2021; Infante 2015; Paci 2017; Pastorino 2012; Wille 2016). LaRocca 2002 did not state if any protocol was used, however NLST (Aberle 2011) and LSS (Gohagan 2005) stated they did not use a trial-wide algorithm for nodule follow-up. Nodule management for each trial is described in Table 1.

Of the 11 trials, nine had a primary outcome that included lung cancer-related mortality (Aberle 2011; Becker 2020; De Koning 2020; Field 2021; Infante 2015; LaRocca 2002; Paci 2017; Pastorino 2012; Wille 2016). The LSS trial had the primary outcome of feasibility to enrol participants in a lung cancer screening programme (Gohagan 2005), however it also had outcomes assessing harms of screening, such as extent of diagnostic follow-up after abnormal screening findings. The DEPISCAN trial also had primary feasibility outcomes of enrolling participants in a lung cancer screening programme (Blanchon 2007), but also outcomes on harms and adverse events during diagnostic procedures, as well as number of futile thoracotomies for benign lesions.

Excluded studies

We excluded 30 studies for the following reasons.

- Irrelevant trial design: 19 studies were not RCTs (Brodersen 2014; Dawson 2020; Favre 2003; Fink 2012; Goulart 2013; Hassannezhad 2018; Henschke 2000; Henschke 2002; Henschke 2015; Horeweg 2013; Kramer 2011; Kulaga 2007; NCT02431962; Robbins 2019; Schabath 2019; Schreuder 2021; Strauss 2012; Strauss 2015; Yip 2013).
- Irrelevant intervention: seven studies did not have LDCT screening alone as an intervention (Bradley 2021; ISRCTN42704678; Marcus 2006; Spiro 2019; Sullivan 2019; Sullivan 2021; Yang 2008). Two papers related to the Yorkshire Lung Screening Trial (lung health check versus usual care) (Bradley 2021; ISRCTN42704678). Marcus 2006 compared CXR and sputum cytology to usual care. Spiro 2019 compared sputum cytology and cytometry to usual care. Two papers compared serum biomarker to usual care (Sullivan 2019; Sullivan 2021). Yang 2008 compared serum biomarker and LDCT with usual care.
- Irrelevant outcomes: one trial measured feasibility of conducting a RCT for lung cancer screening (Garg 2002). Another paper evaluated the effects of computer-aided diagnosis on lung imaging reporting (Park 2022).
- One trial was a duplicate (de-Torres 2021).
- Irrelevant patient population: one trial included participants with a recent diagnosis of lung cancer (Guldbrandt 2015).

Details of these citations are provided in Characteristics of excluded studies.

Risk of bias in included studies

We performed the risk of bias assessment for all included trials with the Cochrane RoB 1 tool (Higgins 2017), and summarised the results in Characteristics of included studies, Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

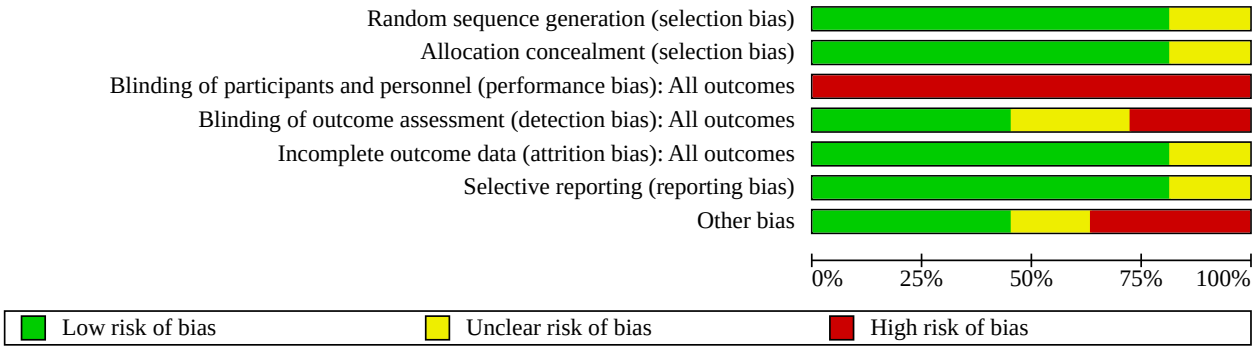
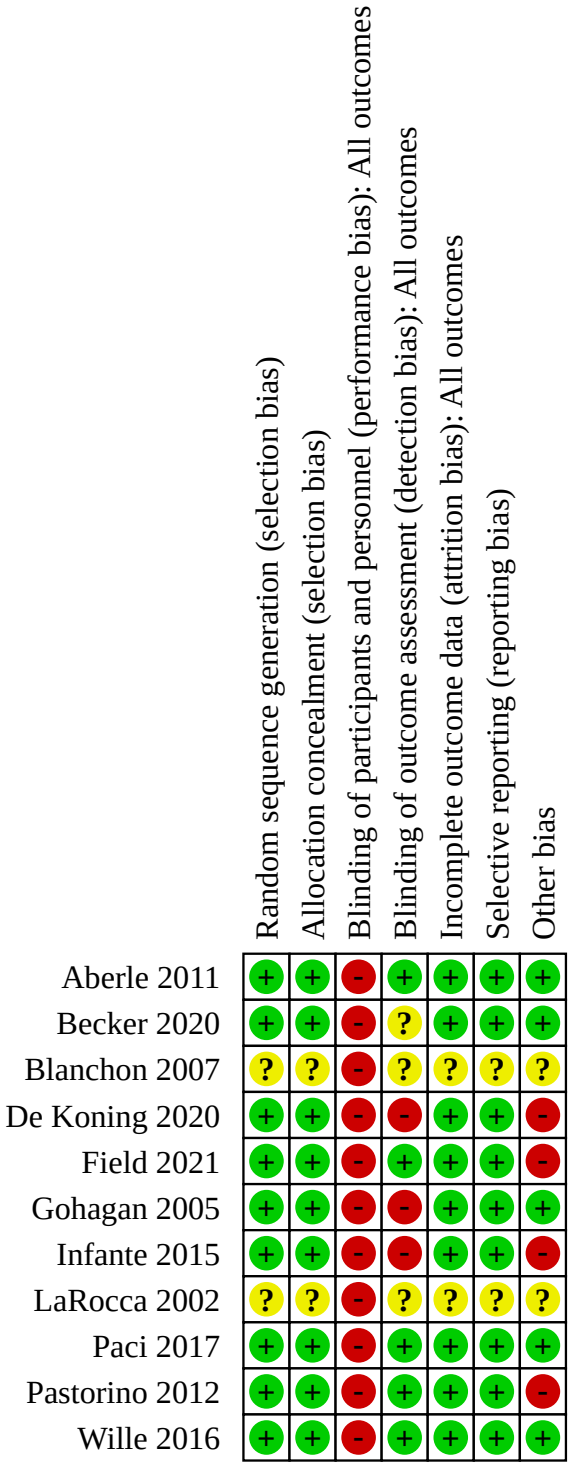


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

We deemed allocation concealment adequate in nine of the 11 trials, suggesting a low risk of bias (Aberle 2011; Becker 2020; Field 2021; Gohagan 2005; Infante 2015; Paci 2017; Pastorino 2012; Wille 2016; De Koning 2020). The remaining two trials had unclear risk of bias (Blanchon 2007; LaRocca 2002), with insufficient information available to determine if a centralised process was used.

We judged sequence generation adequate in nine of the 11 trials, suggesting low risk of bias (Aberle 2011; Becker 2020; Field 2021; Gohagan 2005; Infante 2015; Paci 2017; Pastorino 2012; Wille 2016; De Koning 2020). The remaining two trials had unclear risk of bias (Blanchon 2007; LaRocca 2002), with insufficient information available to determine if a random method in sequence generation was used.

Blinding

Due to the nature of the intervention, no trial participants were blinded to their trial arm in included trials. For this review, lack of blinding of participants in the primary outcomes (lung cancer-related mortality and harms of screening) was unlikely to influence the outcomes. Blinding of assessors for the primary outcome of lung cancer-related mortality was assessed as adequate in five of the 11 trials (Aberle 2011; Field 2021; Pastorino 2012; Paci 2017; Wille 2016). The UKLS trial (Field 2021) only assessed cause of death from registries and death certificates, without the use of a review board.

Two trials did not provide information regarding blinding of assessors (Blanchon 2007; LaRocca 2002), and we judged these at unclear risk. We also deemed Becker 2020 at unclear risk of bias; whilst the assessors in the trial were blinded to the arm when assessing lung cancer-related mortality, the method of identification of lung cancer was not uniform, with 11 of the 67 cases in the control arm and 1 of the 85 cases in the intervention arm detected on death certificate only.

We deemed three of the 11 trials at high risk of bias (De Koning 2020; Gohagan 2005; Infante 2015): neither the LSS (Gohagan 2005) nor the DANTE trial (Infante 2015) blinded assessors; LSS (Gohagan 2005) only assessed cause of death from death certificates, without the use of a review board; and the NELSON trial (De Koning 2020) raised concerns regarding the method of assessing lung cancer as the cause of death - it changed from using a death review panel to using death certificates only during active follow-up, with assessors also unblinded in 2018.

Some outcome measurements, such as all-cause mortality, were not likely to be influenced by lack of blinding.

Incomplete outcome data

Missing data and withdrawals were adequately described in nine of the 11 included trials (Aberle 2011; Becker 2020; De Koning 2020; Field 2021; Gohagan 2005; Infante 2015; Paci 2017; Pastorino 2012; Wille 2016), with risk of bias deemed low risk. Of note, the NLST (Aberle 2011) included 192 participants in their analysis that were deemed ineligible for the trial post-randomisation, and at the end of December 2009 completed active follow-up (meaning the remaining causes of death were assessed as per the registries). The LSS (Gohagan 2005) excluded the 91 participants found to be ineligible post-randomisation from analysis. The ITALUNG trial (Paci 2017) had moderate rates of dropout and non-adherence (81% adherence to screening), however used intention-to-treat analysis. The remaining two trials had insufficient information available to make a judgement and we deemed them at unclear risk (Blanchon 2007; LaRocca 2002).

Selective reporting

We judged nine of the 11 included trials at low risk of reporting bias (Aberle 2011; Becker 2020; De Koning 2020; Field 2021; Gohagan 2005; Infante 2015; Paci 2017; Pastorino 2012; Wille 2016). Whilst the NELSON (De Koning 2020) trial has not published their cost-analysis data, information from the authors confirmed intention to do so. We judged the remaining two trials at unclear risk due to insufficient data available (Blanchon 2007; LaRocca 2002).

Other potential sources of bias

There were minimal deviations to protocols and balanced baselines in five of the 11 trials - we deemed these at low risk of other bias (Aberle 2011; Becker 2020; Gohagan 2005; Paci 2017; Wille 2016). The DLCST (Becker 2020) reported a difference in baseline characteristics between the two groups in mean forced expiratory ratio (FER) (although no difference in mean forced expiratory volume in 1 second (FEV_1)) and number of participants with > 35 pack-year smoking history, however we judged the size of difference unlikely to have had a significant impact on outcomes. Blanchon 2007 and LaRocca 2002 both had insufficient data published to enable us to make an assessment and we judged these at unclear risk of bias. We judged four of the 11 trials at high risk of other bias (De Koning 2020; Field 2021; Infante 2015; Pastorino 2012). We deemed the NELSON (De Koning 2020) trial at high risk of bias due to a change in method of determining lung cancer-related death during the trial, as well as additional amendments to the protocol to add a scan interval of 2.5 years after trial commencement. The trial also did not recruit any women in the Netherlands arm of the trial. Similarly, in the DANTE (Infante 2015) trial women were excluded, and there was an unbalanced baseline between trial arms with respiratory comorbidity more prevalent in the LDCT arm. The UKLS (Field 2021) trial excluded 87 participants from long-term mortality and incidence analysis and did not use intention-to-screen analysis, however we judged the number of participants was likely too small to have an impact on results. It should be noted that LLPv2 was unintentionally used rather than LLPv1 as the risk prediction model in UKLS (Field 2021). The MILD (Pastorino 2012) trial had an unbalanced baseline between arms with 90% of the control arm being current smokers compared with 69% of the LDCT arm. Additionally, when the MILD (Pastorino 2012) trial commenced recruitment, there was only the annual LDCT and biennial LDCT groups, with the no-screening control group added later.

Effects of interventions

See: **Summary of findings 1** Low-dose computed tomography (LDCT) screening compared to no LDCT screening for lung cancer-related mortality

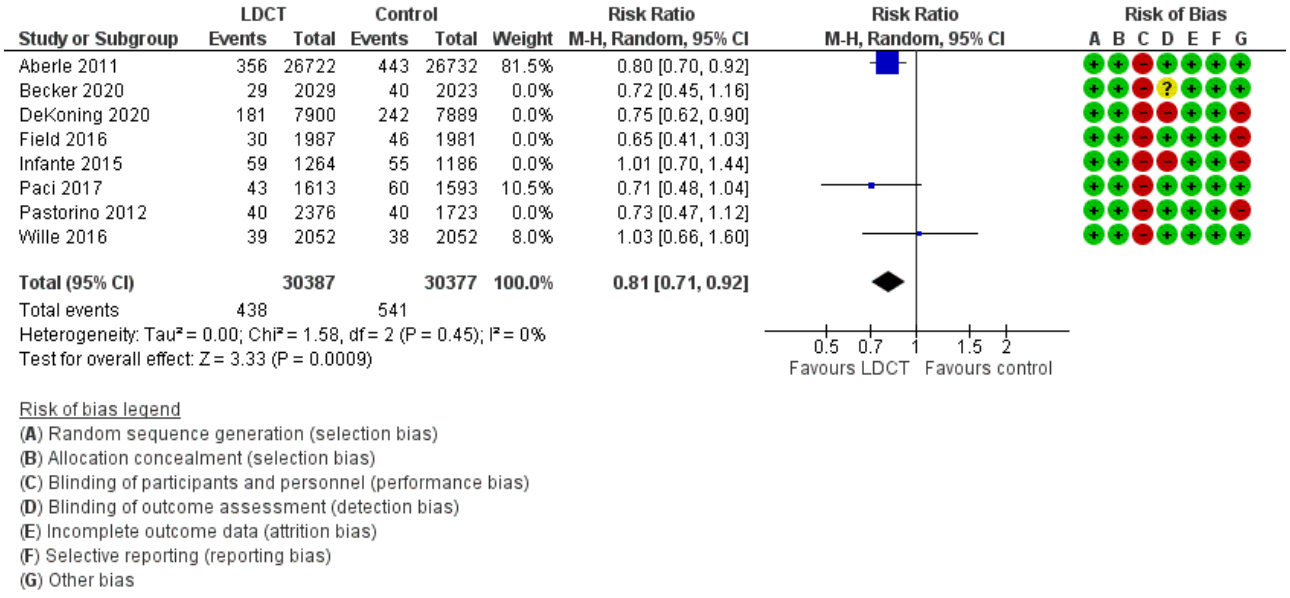
Primary outcomes

1) Lung cancer-related mortality

Lung cancer-related mortality using planned follow-up time points

We pooled the latest time point for planned lung cancer-related mortality for all available trials. We included eight trials in this analysis (Aberle 2011; Becker 2020; De Koning 2020; Field 2021; Infante 2015; Paci 2017; Pastorino 2012; Wille 2016). Time points (median time post-randomisation) for these trials were 6.5 years, 8.8 years, 10 years, 7 years, 8.5 years, 9.3 years, 10 years, and 10 years respectively. We did not include the LSS (Gohagan 2005) as the planned follow-up for the trial was only 2 years. The evidence showed a difference in lung cancer-related mortality favouring screening with LDCT, with a reduction in lung cancer-related mortality of 21% (risk ratio (RR) 0.79, 95% confidence interval (CI) 0.72 to 0.87; 8 trials, 91,122 participants; I^2 = 0%; moderate-certainty evidence; Analysis 1.1). The number needed to screen to prevent one additional lung cancer-related death was 226. The NLST (Aberle 2011) and NELSON (De Koning 2020) trials both had strong weighting in this analysis, with the DLCST (Wille 2016), and DANTE (Infante 2015) trials demonstrating probably no difference with LDCT screening on lung cancer-related mortality. When we performed sensitivity analysis using three trials with low risk of bias (Aberle 2011; Paci 2017; Wille 2016), the evidence still favoured screening, with a reduction in lung cancer-related mortality (RR 0.81, 95% CI 0.71 to 0.92; 3 trials, 60,764 participants; I^2 = 0%; high-certainty evidence; Figure 4). The number needed to screen to prevent one additional lung cancer-related death was 296.

Figure 4. Lung cancer mortality - Planned time points - Sensitivity analysis



When we analysed hazard ratios (HRs) from Becker 2020, Infante 2015, and Wille 2016 at the > 8 to 10-year planned follow-up time point post-randomisation, there was probably no difference for people at risk for lung cancer-related mortality with LDCT screening (HR 0.93, 95% CI 0.72 to 1.19; 3 trials, 10,606 participants; I^2 = 0%; Analysis 1.2).

Lung cancer-related mortality using planned and unplanned follow-up time points

We also grouped trial results by time points, including planned and unplanned extended follow-up, as depicted in Analysis 1.3.

- 5 to 6 years post-randomisation: four RCTs reported this outcome at this time point (Becker 2020; De Koning 2020; Gohagan 2005; Wille 2016). There was probably no difference between LDCT and control groups in relation to lung cancer-related mortality (RR 0.89, 95% CI 0.64 to 1.24; 4 trials, 27,263 participants; I^2 = 42%). Heterogeneity amongst trials was moderate, but within acceptable limits. On average, 466 people would have to be screened to prevent one additional lung cancer-related death.
- More than 6 to 8 years post-randomisation: we included three RCTS (Aberle 2011; De Koning 2020; Field 2021). The evidence showed there was a difference in lung cancer-related mortality favouring LDCT screening over no screening (RR 0.77, 95% CI 0.69 to 0.86; 3 trials, 73,211 participants; I^2 = 0%). On average, 233 people would have to be screened to prevent one additional death related to lung cancer.
- More than 8 to 10 years post-randomisation: we included six RCTs (Becker 2020; De Koning 2020; Infante 2015; Paci 2017; Pastorino 2012; Wille 2016), and once more, pooling data showed a difference favouring LDCT screening in lung cancer-related mortality (RR 0.79, 95% CI 0.69 to 0.90; 6 trials, 33,700 participants; I^2 = 0%). Of note, screening in DANTE (Infante 2015) and DLCST (Wille 2016) probably made no difference, however they were smaller trials. The MILD (Pastorino 2012) trial combined both biennial and annual trial group mortality data for the outcome. On average, 163 people would have to be screened to prevent one additional death from lung cancer.
- More than 10 years post-randomisation: we included three RCTS (Aberle 2011; De Koning 2020; Paci 2017), and the evidence showed a difference favouring LDCT screening in lung cancer-related mortality (RR 0.86, 95% CI 0.75 to 0.98; 3 trials, 72,447

participants; I^2 = 48%). Heterogeneity amongst trials was moderate, but within acceptable limits. On average, 222 people would have to be screened to prevent one additional death from lung cancer.

Lung cancer-related mortality by time postcompletion of screening

We grouped trial results by years postcompletion of screening using planned and unplanned time point follow-up data from all nine available trials (Aberle 2011; Becker 2020; De Koning 2020; Field 2021; Gohagan 2005; Infante 2015; Paci 2017; Pastorino 2012; Wille 2016) in Analysis 1.5. When multiple time points were available for a trial within one bracket of time, we used the latest time point data.

- Zero to 1 year postscreening completion: we included four RCTs (Becker 2020; De Koning 2020; Pastorino 2012; Wille 2016). The evidence showed a difference in lung cancer-related mortality favouring screening (RR 0.76, 95% CI 0.61 to 0.94; 4 trials, 28,044 participants; I^2 = 0%). On average, 324 people would need to be screened to prevent one additional death related to lung cancer.
- 2 to 4.5 years postscreening completion: we included five RCTs (Aberle 2011; Becker 2020; De Koning 2020; Gohagan 2005; Infante 2015). The evidence favoured LDCT screening for lung cancer-related morality (RR 0.82, 95% CI 0.72 to 0.93; 5 trials, 79,063 participants; I^2 = 18%). On average, 262 people would need to be screened to prevent one additional death from lung cancer-related mortality.
- 5 to 7 years postscreening completion: we included four RCTs (De Koning 2020; Field 2021; Paci 2017; Wille 2016). The evidence favoured screening for lung cancer-related mortality (RR 0.78, 95% CI 0.67 to 0.90; 4 trials, 27,067 participants; I^2 = 0%). On average, 149 people would need to be screened to prevent one additional death related to lung cancer.
- More than 7 to 10 years postscreening completion: we included two RCTs (Aberle 2011; Paci 2017). There was probably no difference between the groups for lung cancer-related mortality (RR 0.92, 95% CI 0.83 to 1.01; 2 trials, 56,658 participants; I^2 = 6%).

Lung cancer-related mortality by different subgroups

- **By screening arm**

Planned time periods: we pooled lung cancer-related mortality data from all eight available trials and divided the data into subgroups based on control arm comparator, CXR (Aberle 2011) or no screening (Becker 2020; De Koning 2020; Field 2021; Infante 2015; Paci 2017; Pastorino 2012; Wille 2016), using the latest planned follow-up time point for each trial in Analysis 1.4.

1. For usual care: the evidence showed a difference in lung cancer-related mortality favouring screening when compared to usual care (RR 0.78, 95% CI 0.69 to 0.88; 7 trials, 37,668 participants; I^2 = 0%).
2. For CXR: the evidence also favoured LDCT over CXR (RR 0.80, 95% CI 0.70 to 0.92; 1 trial, 53,434 participants).

There was no difference between subgroups. Test for subgroup differences: Chi^2 = 0.11, df = 1 (P = 0.74), I^2 = 0% (Analysis 1.4).

- **By screening intervals**

We also presented the latest planned time point data from nine available trials by screening interval in Analysis 1.6. The MILD trial (Pastorino 2012) had mortality data presented separately by intervention group (biennial and annual). The NELSON (De Koning 2020) trial, with incremental intervals, demonstrated a reduction in lung cancer-related mortality (RR 0.75, 95% CI 0.62 to 0.90; 1 trial, 15,789 participants), while data from NLST (Aberle 2011), which had three annual screens also favoured LDCT (RR 0.80, 95% CI 0.70 to 0.92; 1 trial, 53454 participants). The overall results favoured LDCT screening for lung cancer-related mortality (RR 0.79, 95% CI 0.72 to 0.87; 9 trials, 91,122 participants; I^2 = 0), with no subgroup difference (test for subgroup differences: Chi^2 = 3.38, df = 6 (P = 0.76), I^2 = 0%).

- **By sex**

Five trials reported mortality due to lung cancer by sex (Aberle 2011; Becker 2020; De Koning 2020; Field 2021; Infante 2015), as depicted in Analysis 1.8 and Analysis 1.7.

1. For women: we included four RCTS (Aberle 2011; Becker 2020; De Koning 2020; Field 2021). We used data from the latest planned time point available for this analysis. The evidence showed a difference in lung cancer-related mortality in women favouring LDCT screening, and screening reduced the risk by 29% (RR 0.71, 95% CI 0.59 to 0.86; 4 trials, 26,965 participants; I^2 = 0%; Analysis 1.8). However, the pooled HRs from three RCTs showed screening reduced the risk of death by 27% compared to no screening (HR 0.73, 95% CI 0.34 to 1.56; 3 trials, 4286 participants; I^2= 64%; Analysis 1.7). However, the 95% CI included 1, so there was probably no difference between the two arms. Removing Wille 2016, reduced the heterogeneity between trials without changing the finding (HR 0.50, 95% CI 0.23 to 1.07; 2 trials, 2449 participants; I^2=15%) (analysis not shown).
2. For men: we included five RCTS (Aberle 2011; Becker 2020; De Koning 2020; Field 2021; Infante 2015). We used data from the latest planned time point available for this analysis. The evidence showed a difference in lung cancer-related mortality in men favouring LDCT screening, and screening reduced risk by 15% (RR 0.85, 95% CI 0.76 to 0.95; 5 trials, 52,833 participants; I^2 = 0%; Analysis 1.8). Analysis of HRs (HR 0.76, 95% CI 0.52 to 1.12; 2 trials, 5658 participants) demonstrated that screening could reduce the risk of death by 24% compared to no screening among men, however the 95% CI included 1, so there was probably no difference for men at risk for lung cancer-related mortality with LDCT screening (Analysis 1.7).

There was no difference between the two subgroups. Test for subgroup differences: Chi^2 = 2.49, df = 1 (P = 0.11), I^2 = 59.9%.

- **By age**

One trial (Aberle 2011) presented mortality data by age group for the latest planned time point Analysis 1.9.

1. For those < 65 years old: the evidence favoured LDCT screening to reduce lung cancer-related mortality by 18% (RR 0.82, 95% CI 0.70 to 0.97; 1 trial, 39,234 participants).
2. For those ≥ 65 years: the evidence favoured LDCT screening to reduce lung cancer-related mortality by 38% (RR 0.62, 95% CI 0.52 to 0.74; 1 trial, 17,218 participants).

- **By smoking status**

Only one trial (Aberle 2011) presented lung cancer-related mortality data by smoking status (former or current). Data from both 6.5 years and 12.3 years post-randomisation are provided in Analysis 1.10. At both time points, the evidence showed a benefit in LDCT screening for lung cancer-related mortality in current smokers (6.5 years: RR 0.82, 95% CI 0.70 to 0.95; 1 trial, 25,760 participants; I^2 = 0%) and (12.3 years: RR 0.89, 95% CI 0.81 to 0.98; 1 trial, 25,760 participants). However, evidence suggested there was probably no difference in former smokers (6.5 years: RR 0.91, 95% CI 0.74 to 1.11; 1 trial, 27,692 participants) and (12.3 years: RR 1.01, 95% CI 0.88 to 1.15; 1 trial, 27,692 participants).

The DLCST (Wille 2016) presented lung cancer-related mortality by number of pack years smoked < 35 or ≥ 35, there was probably no difference between the groups, for < 35 pack years (RR 1.26, 95% CI 0.55 to 2.90; 1 trial, 2148 participants) and ≥ 35 pack years (RR 0.92, 95% CI 0.54 to 1.54; 1 trial, 1955 participants) in this trial (Analysis 1.10).

- **By geographical regions**

Planned time points: lung cancer-related mortality by geographical region using the latest planned time point is presented in Analysis 1.11.

1. Europe: we included seven trials (Becker 2020; De Koning 2020; Field 2021; Infante 2015; Paci 2017; Pastorino 2012; Wille 2016). The evidence demonstrated a benefit in lung cancer-related mortality with LDCT screening (RR 0.78, 95% CI 0.69 to 0.88; 7 trials, 37,668 participants; I^2 = 0%).
2. USA: we included one trial (Aberle 2011). The evidence demonstrated a benefit in lung cancer-related mortality with LDCT screening (RR 0.80, 95% CI 0.70 to 0.92; 1 trial, 53,454 participants).

This analysis (Analysis 1.11) is identical to Analysis 1.4, as the USA trial was the only one to use CXR as a comparison. Overall, the evidence suggested a lung cancer-related mortality benefit with LDCT screening.

There was no difference between the groups. Test for subgroup differences: Chi^2 = 0.11, df = 1 (P = 0.74), I^2 = 0%.

- **By algorithms for nodule management**

We also grouped trials by use of trial-wide algorithms for nodule management (yes or no) using the latest planned time points in Analysis 1.12.

1. Yes: we included six RCTs (Becker 2020; De Koning 2020; Field 2021; Paci 2017; Pastorino 2012; Wille 2016). The evidence suggested a difference in lung cancer-related mortality favouring screening in this group (RR 0.75, 95% CI 0.66 to 0.86; 6 trials, 35,218 participants; I^2 = 0%). We also applied a fixed-effect model for analysis and the conclusion was the same (RR 0.75, 95% CI 0.66 to 0.86; 6 trials, 35,218 participants; I^2 = 0%).
2. No: we included two trials (Aberle 2011; Infante 2015). There was probably no difference using a random-effects model for analysis (RR 0.84, 95% CI 0.70 to 1.01; 2 trials, 55,904 participants; I^2 = 24%). However, when we applied a fixed-effect model, the evidence showed a difference in lung cancer-related mortality favouring screening (RR 0.83, 95% CI 0.73 to 0.94; 2 trials, 55,904 participants; I^2 = 24%).

There was no difference between the groups. Test for subgroup differences: Chi^2 = 1.02, df = 1 (P = 0.31), I^2 = 2.2%.

- **By nodule analysis method**

We grouped trials by method of nodule analysis (diameter criteria and/or volumetric criteria) using the latest planned time points in Analysis 1.13.

1. Diameter criteria: we included three RCTs (Aberle 2011; Infante 2015; Paci 2017). The evidence showed a difference in lung cancer-related mortality favouring screening (RR 0.81, 95% CI 0.72 to 0.92; 3 trials, 59,110 participants; I^2 = 0%).
2. Volume criteria: we included two RCTs (De Koning 2020; Pastorino 2012). The evidence showed a difference in lung cancer-related mortality favouring screening (RR 0.74, 95% CI 0.62 to 0.88; 2 trials, 19,888 participants; I^2 = 0%).
3. Diameter and volume criteria: we included three trials (Becker 2020; Field 2021; Wille 2016). These trials demonstrated there was probably no difference between the groups (RR 0.79, 95% CI 0.60 to 1.04; 3 trials, 12,124 participants; I^2 = 8%). It should be noted that all included trials had low participant numbers.

There was no difference between the groups. Test for subgroup differences: Chi^2 = 0.71, df = 2 (P = 0.70), I^2 = 0%. Nodule management pathways are detailed in Table 1.

2) Harms of screening

Number of all invasive tests performed

We grouped trial results based on time point (following baseline screening scan or at follow-up) (Analysis 2.1).

- At baseline: we included three RCTs (Aberle 2011; Gohagan 2005; Infante 2015). We combined invasive procedures and surgery numbers provided in Infante 2015 for this analysis. The evidence showed that more invasive tests were performed in the LDCT screening group (RR 2.90, 95% CI 2.25 to 3.75; 3 trials, 59,110 participants; I^2 = 43%); 363 invasive tests were performed for every 10,000 participants screened with LDCT, with a number needed to harm (NNH) of 44. Heterogeneity was moderate, and when we removed Aberle 2011 from the analysis, there was no heterogeneity and no change to the conclusion (RR 3.56, 95% CI 2.53 to 5.01; 2 trials, 5768 participants; I^2 = 0%) (analysis not shown). Both NLST (Aberle 2011) and LSS (Gohagan 2005) had CXR screening as a comparison, whilst the DANTE (Infante 2015) trial performed a CXR and sputum cytology in both groups prior to screening.
- At follow-up: we included three RCTs (Aberle 2011; Infante 2015; Pastorino 2012). The evidence showed that more invasive tests were performed in the LDCT screening group (RR 2.60, 95% CI 2.41 to 2.80; 3 trials, 60,003 participants; I^2 = 0%; moderate-certainty evidence). The data we used in the analysis for MILD trial (Pastorino 2012) was only inclusive of surgery cases; 788 invasive tests occurred for every 10,000 participants screened with LDCT (NNH = 21). The MILD trial (Pastorino 2012) was the only trial that had no CXRs performed in the control group.

There was no difference between the subgroups. Test for subgroup differences: Chi^2 = 0.67, df = 1 (P = 0.41), I^2 = 0%.

Whilst DESPICAN (Blanchon 2007) included adverse events during diagnostic procedures and number of thoracotomies for benign disease, it did not specify the participant groups when presenting results and subsequently we did not include it in our analysis of harms of screening.

Number of all non-invasive tests performed

We grouped trial results based on time point (following baseline screening scan or at follow-up) (Analysis 2.2).

- At baseline: we included three RCTs (Aberle 2011; Gohagan 2005; Infante 2015). The evidence showed that more non-invasive tests were performed in the LDCT screening group (RR 3.28, 95% CI 2.40 to 4.48; 3 trials, 59,222 participants; I^2 = 90%) (analysis not shown). Heterogeneity was high, with a slight reduction to 70% when we removed Infante 2015 (RR 2.68, 95% CI 2.30 to 3.12; 2 trials, 56,772 participants; I^2 = 70%); 2154 non-invasive tests would be performed for every 10,000 people screened with LDCT (NNH = 7). Of note, Infante 2015 was the only included trial that did not have CXR screening in the control arm, although participants did receive one at baseline. The DANTE (Infante 2015) trial included additional CT and PET scans, whilst Gohagan 2005 included pulmonary function tests, CT and CXR. The NLST (Aberle 2011) combined all additional imaging numbers, and hence heterogeneity was clinical.
- At follow-up: we included two RCTs which reported additional PET scans (Aberle 2011; Infante 2015). The evidence also showed that more non-invasive tests were performed in the LDCT screening group (RR 3.56, 95% CI 1.81 to 7.01; 2 trials, 55,905 participants; I^2 = 86%) (analysis not shown).

There was no difference between the subgroups. Test for subgroup differences: Chi^2 = 0.05, df = 1 (P = 0.83), I^2 = 0%).

Number of invasive tests performed in those with a false-positive diagnosis (positive test in the absence of lung cancer)

We grouped trial results based on time point (following baseline screening scan or at follow-up) (Analysis 2.3).

- At baseline: we only included one RCT (Gohagan 2005). The invasive interventions included bronchoscopy and biopsies, with a higher rate of intervention in the screening group (RR 3.09, 95% CI 1.57 to 6.07; 3318 participants; 1 trial; I^2 = 0%); 205 invasive tests would be performed for false-positive results for every 10,000 participants screened at baseline (NNH = 72).
- At follow-up: we included three RCTs (Aberle 2011; Infante 2015; Pastorino 2012). The NLST (Aberle 2011) included thoracotomy, bronchoscopy, and needle biopsy, whereas Infante 2015 and Pastorino 2012 included only surgery numbers for invasive procedures. The MILD (Pastorino 2012) intervention arm was the combined total of the biennial and annual screening groups. The evidence showed that more invasive tests were performed in the LDCT screening group (RR 3.91, 95% CI 3.21 to 4.76; 3 trials, 60,005 participants; I^2 = 0%); 159 invasive tests would be performed in false-positive results for every 10,000 participants screened (NNH = 85).

There was no difference between the subgroups. Test for subgroup differences: Chi^2 = 0.43, df = 1 (P = 0.51), I^2 = 0%. Invasive tests performed in non-lung cancer-related disease are summarised in Table 2.

There were no common time points for non-invasive tests performed in participants without lung cancer, however we compared total numbers in both groups in two RCTs (Aberle 2011; Gohagan 2005).

Any complications arising from tests including death

Two RCTs which reported mortality rates within 60 days of surgery (Aberle 2011; Infante 2015). The NSLT (Aberle 2011) had a CXR screening comparison arm, whereas the DANTE trial (Infante 2015) had a baseline CXR and sputum cytology for all participants followed by annual clinical examinations. There was probably no difference in mortality following surgery between the groups (RR 0.68, 95% CI 0.24 to 1.94; 2 trials, 409 participants; I^2 = 0%; moderate-certainty evidence; Analysis 2.4). Another RCT also reported postsurgery mortality rates (Paci 2017), however we were unable to locate the total number of surgeries in each group and consequently, we did not include it in the analysis.

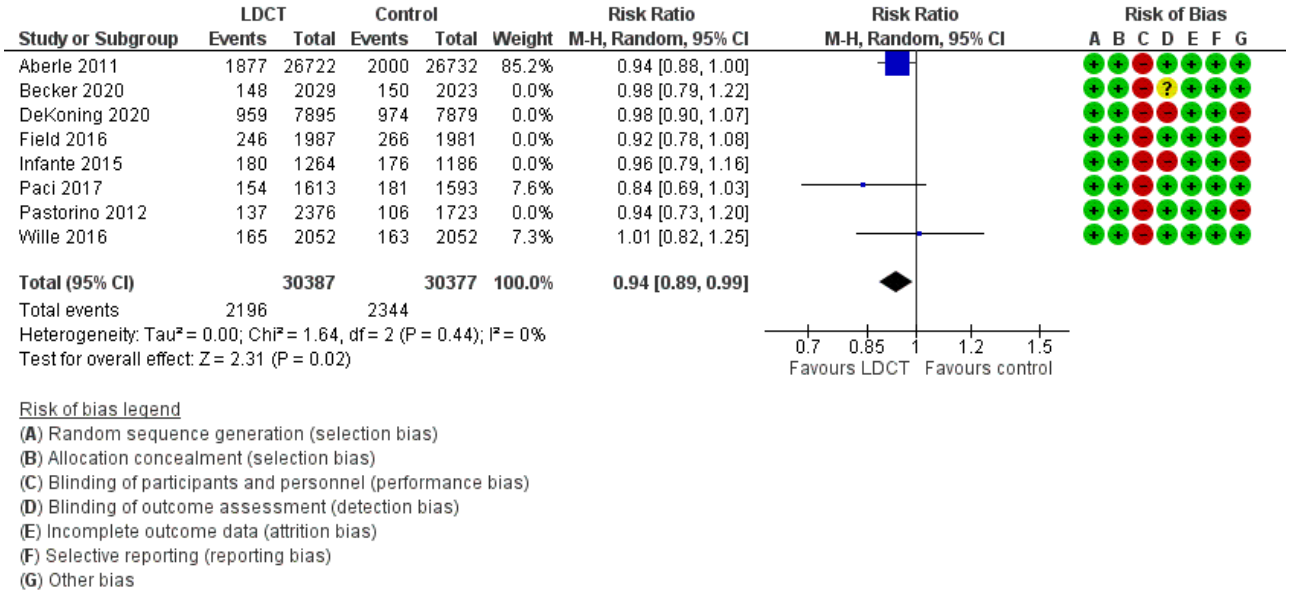
We reported a comparison of complications arising from tests for non-cancer-related disease in two RCTs at different time points (Aberle 2011; Gohagan 2005).

Secondary outcomes

3) All-cause mortality

We combined trial data from all eight available trials using the latest planned follow-up time point for each trial (Aberle 2011; Becker 2020; De Koning 2020; Field 2021; Infante 2015; Paci 2017; Pastorino 2012; Wille 2016; see Analysis 3.1). We excluded the LSS (Gohagan 2005) from this analysis as it did not have planned follow-up at ≥ 5 years. The evidence showed a 5% risk reduction in all-cause mortality with LDCR screening (RR 0.95, 95% CI 0.91 to 0.99; 8 trials, 91,107 participants; I^2 = 0%; moderate-certainty evidence); 210 people would need to be screened to prevent one death from all-cause mortality. When we performed a sensitivity analysis using trials with low risk of bias (Aberle 2011; Paci 2017; Wille 2016), there was probably a difference between the groups for all-cause mortality favouring LDCT (RR 0.94, 95% CI 0.89 to 0.99; 3 trials, 60,764 participants; I^2 = 0%); 204 people would need to be screened to prevent one death from all-cause mortality (Figure 5). When we analysed HRs from Becker 2020, Infante 2015 and Wille 2016 at the latest planned time points post-randomisation, there was probably no difference for people at risk for all-cause mortality with LDCT screening (HR 0.98, 95% CI 0.87 to 1.12; 3 trials, 10,606 participants; I^2 = 0%; Analysis 3.3).

Figure 5. All-cause mortality - Planned time points - Sensitivity analysis



We also grouped trial results by time points (planned and unplanned) (Analysis 3.2).

- 5 to 6 years post-randomisation: we included three RCTS (Becker 2020; Gohagan 2005; Wille 2016). There was probably no difference between LDCT and control groups in all-cause mortality (RR 1.14, 95% CI 0.88 to 1.47; 3 trials, 11,474 participants; I^2 = 52%). There was moderate heterogeneity, which disappeared when we excluded the results from Becker 2020 (RR 1.26, 95% CI 1.03 to 1.54; 2 trials, 7422 participants; I^2 = 0%).
- More than 6 to 8 years post-randomisation: we included two RCTs (Aberle 2011; Field 2021). The evidence showed there was a difference in all-cause mortality favouring LDCT screening (RR 0.94, 95% CI 0.89 to 0.99; 2 trials, 57,422 participants; I^2 = 0%).
- More than 8 to 10 years post-randomisation: we included six RCTS (Becker 2020; De Koning 2020; Infante 2015; Paci 2017; Pastorino 2012; Wille 2016). There was probably no difference between LDCT and control groups in all-cause mortality (RR 0.97, 95% CI 0.91 to 1.03; 6 trials, 33,685 participants; I^2 = 0%).
- More than 10 years post-randomisation: we included two RCTs (Aberle 2011; Paci 2017). There was probably no difference between LDCT and control groups in all-cause mortality (RR 0.91, 95% CI 0.76 to 1.09; 2 trials, 56,658 participants; I^2 = 76%). Heterogeneity between the two trials was high, with ITALUNG (Paci 2017) favouring screening. It should be noted that the NLST (Aberle 2011) had CXR as a comparison.

All-cause mortality by different subgroups (planned time points)

- **By sex**

Three trials reported mortality by sex (Aberle 2011; De Koning 2020; Infante 2015); see Analysis 3.4.

For women: we included two RCTs (Aberle 2011; De Koning 2020). The NELSON trial (De Koning 2020) results for women were not provided and so we calculated these from available data. There was probably no difference between LDCT and control groups in all-cause mortality and heterogeneity was moderate (RR 0.89, 95% CI 0.76 to 1.03; 2 trials, 24,514 participants; I^2 = 31%).

For men: we included three RCTs (Aberle 2011; De Koning 2020; Infante 2015). The evidence showed there was no difference in all-cause mortality (RR 0.93, 95% CI 0.80 to 1.07; 3 trials, 49,162 participants; I^2 = 82%) (analysis not shown). Heterogeneity was high, with Aberle 2011 having significant weight in the analysis. When we removed Aberle 2011, there was no heterogeneity, however data suggested there was probably no difference between LDCT and control groups in all-cause mortality (RR 1.00, 95% CI 0.93 to 1.09; 2 trials, 5632 participants; I^2 = 0%).

There was no difference between the two groups. Test for subgroup differences: Chi^2 = 1.96, df = 1 (P = 0.16), I^2 = 48.9%.

- **By cause of death:** two trials reported cardiovascular mortality (Becker 2020; Paci 2017), and we grouped these by time points (Analysis 3.5).

At 8 to 10 years planned time points: we included two RCTS (Becker 2020; Paci 2017) and the data was collected as part of their planned analysis. There was probably no difference between LDCT and control groups in cardiovascular-related mortality and heterogeneity was high (RR 0.76, 95% CI 0.37 to 1.56; 2 trials, 7258 participants; I^2 = 78%) (analysis not shown).

At more than 10 years using unplanned time points, we included only one RCT (Paci 2017). The evidence showed there was a difference in cardiovascular mortality favouring LDCT screening (RR 0.53, 95% CI 0.34 to 0.81; 1 trial, 3206 participants).

4) Lung cancer incidence and overdiagnosis

Lung cancer incidence

We grouped trial results by time points (planned and unplanned) (Analysis 4.1).

- At baseline: we included six trials (Aberle 2011; Blanchon 2007; De Koning 2020; Gohagan 2005; Infante 2015; Wille 2016). The evidence showed a higher incidence of lung cancer in the LDCT screening group, (RR 4.98, 95% CI 2.01 to 12.35; 6 trials, 79,900 participants; I^2 = 87%), with high heterogeneity. Removing Aberle 2011 reduced the heterogeneity to a moderate level (RR 6.45, 95% CI 3.21 to 12.98; 5 trials, 26,448 participants; I^2 = 49%). Both the NLST(Aberle 2011) and LSS (Gohagan 2005) had CXR screening in the control arm.
- At 1 year post-randomisation: we included three RCTs (Aberle 2011; De Koning 2020; Wille 2016). The evidence showed a higher incidence of lung cancer in the LDCT screening group, with high heterogeneity (RR 2.12, 95% CI 1.35 to 3.31; 3 trials, 73,345 participants; I^2 = 54%). After removing Aberle 2011, there was no heterogeneity (RR 2.87, 95% CI 1.78 to 4.60; 2 trials, 19,893participants; I^2 = 0%).
- At two years post-randomisation: we included two RCTs (Aberle 2011, Wille 2016). This analysis demonstrated a higher incidence of lung cancer in the LDCT screening group (RR 1.88, 95% CI 1.51 to 2.32; 2 trials, 57,556 participants; I^2 = 0%).
- At 3 years post-randomisation: we included one RCT (Wille 2016). This trial suggested the possibility of no difference in the incidence of lung cancer between the groups (RR 1.71, 95% CI 0.68 to 4.35; 1 trial, 4104 participants; I^2 = 0%)
- At 4 years post-randomisation: we included one RCT (Wille 2016). This trial demonstrated a higher incidence of lung cancer in the LDCT screening group (RR 2.67, 95% CI 1.05 to 6.80; 1 trial, 4104 participants; I^2 = 0%).
- At 5 to 7 years post-randomisation: we included two RCTs (Aberle 2011; Becker 2020). The evidence showed a higher incidence of lung cancer in the LDCT screening group (RR 1.13, 95% CI 1.04 to 1.23; 2 trials, 57,506 participants; I^2 = 0%).
- At more than 7 years post-randomisation: we included eight RCTS (Aberle 2011; Becker 2020; De Koning 2020; Field 2021; Infante 2015; Paci 2017; Pastorino 2012; Wille 2016). Of note, only male participant data were available and included in this analysis for the NELSON trial (De Koning 2020). The MILD (Pastorino 2012) trial had both annual and biennial groups combined into the intervention arm. The evidence showed a higher incidence of lung cancer in the LDCT screening group (RR 1.17, 95% CI 1.02 to 1.33; 8 trials, 8528 participants; I^2 = 65%). Heterogeneity was high, and became low when we removed Wille 2016 from the analysis (RR 1.08, 95% CI 0.99 to 1.18; 7 trials, 84,424 participants; I^2 = 27%) (analysis not shown).

We grouped trials with ≥ 10 years follow-up post-randomisation based on control arm (Analysis 4.2).

- No screening comparison: we included five RCTs (Becker 2020; De Koning 2020; Paci 2017; Pastorino 2012; Wille 2016). There was possibly no difference in lung cancer incidence between the groups (RR 1.21, 95% CI 0.99 to 1.48; 5 trials, 28,656 participants; I^2 = 66%). Heterogeneity was high, which was probably due to the DLCST trial (Wille 2016), which reported less lung cancer in the control group (RR 1.11, 95% CI 0.99 to 1.24; 4 trials, 24,552 participants; I^2 = 0%) (analysis not shown).
- CXR comparison: we included one RCT (Aberle 2011). There was probably no difference in lung cancer incidence between the groups (RR 1.01, 95% CI 0.95 to 1.08; 1 trial, 53,454 participants).

There was no difference between the subgroups. Test for subgroup differences: Chi^2 = 2.62, df = 1 (P = 0.11), I^2 = 61.8%.

Overdiagnosis

Estimates were described by five trials (Aberle 2011; Becker 2020; Field 2021; Paci 2017; Wille 2016), and ranged from -4% to 67% for all lung cancers (Table 3). This was in part due to some adenocarcinoma subtypes We divided overdiagnosis using definitions from the NLST (Aberle 2011) where overdiagnosis from a public health perspective used cumulated lung cancer incidence rate as the denominator, whereas the clinical perspective used screen-detected lung cancer incidence as the denominator.

We estimated overdiagnosis based on the control arm (Analysis 4.3). We calculated estimates from the total incidence in each arm and these were not limited to screen-detected cancers only. Based on extended follow-up (≥ 10 years), calculated rates of overdiagnosis for the NELSON trial (De Koning 2020) was 12%, with a wide CI (95% CI -1% to 25%). It should be noted that extended incidence and hence overdiagnosis was only relevant to male participants in this trial. The estimated overdiagnosis rate of ITALUNG (Paci 2017) was -11%, with a 95% CI of -42% to 20%. The estimated overdiagnosis rate of MILD (Pastorino 2012) was 16%, again with a wide CI (95% CI -10% to 41%). The DLCST (Wille 2016) had an estimated overdiagnosis rate of 47% and had the only CI that did not cross 0 (95% CI 30% to 64%). The NLST compared LDCT to CXR and so we excluded it from the meta-analysis, however it had an estimated overdiagnosis rate of 1% (95% CI -5% to 7%). The DANTE (Infante 2015) trial included CXR and sputum cytology for both trial groups pre-screening, and had a median follow-up of < 10 years, and so we did not include it in the meta-analysis of overdiagnosis. The calculated overdiagnosis rate for the DANTE (Infante 2015) trial was 26% (95% CI 5 to 48%).

Five trials compared LDCT screening with usual care after ≥ 10 years from randomisation (Becker 2020; De Koning 2020; Paci 2017; Pastorino 2012; Wille 2016), with an estimated overdiagnosis rate of 18% (RD 0.18, 95% CI -0.00 to 0.36; 5 trials, 28,656 participants; I^2 = 73%; low-certainty evidence), with a wide CI that does not meet significance (Analysis 4.3). It is estimated that 7 cases of lung cancer overdiagnosis would occur for every 1000 people screened (95% CI of 2 to 84 cases of overdiagnosis). Heterogeneity was also high, and reduced when we removed Wille 2016.

5) False-positive, negative and recall rates

False-positive rates were provided for eight RCTS (Aberle 2011; Becker 2020; Blanchon 2007; De Koning 2020; Field 2021; Gohagan 2005; Pastorino 2012; Wille 2016) and are detailed in Table 3. When we combined all available baseline LDCT results from seven trials (Aberle 2011; Becker 2020; Blanchon 2007; De Koning 2020; Field 2021; Gohagan 2005; Wille 2016), 21% of trial screens had a false-positive result, with a range from 1% to 46%. The false-positive rate of LDCT was lower in trials that used volumetric analysis alone (De Koning 2020; Pastorino 2012), which ranged from 1% to 5%, compared with diameter criteria alone (Aberle 2011; Blanchon 2007; Gohagan 2005) which ranged from 18% to 26%. The three trials that used both diameter and volumetric criteria (Becker 2020; Field 2021; Wille 2016) had false-positive rates of 21%, 46%, and 8%, respectively. Four per cent of participants had false-positive results reviewed in a multidisciplinary team meeting in UKLS (Field 2021). False-positive rates also decreased with subsequent LDCT screens (Aberle 2011; Becker 2020; De Koning 2020; Wille 2016). It should be

noted that false positives in the NELSON trial (De Koning 2020) did not include all participants who had an indeterminate scan, only those who had a positive follow-up scan following an indeterminate result.

When we combined results from all available three trials comparing LDCT and CXR (Aberle 2011; Blanchon 2007; Gohagan 2005) using the latest follow-up time point for each trial (Analysis 5.1), the evidence showed fewer false positives in the CXR groups with high heterogeneity between the trials (RR 2.82, 95% CI 1.98 to 4.01; 3 trials, 56,101 participants; I^2 = 90%) (analysis not shown). Removing Gohagan 2005 reduced the heterogeneity, however the conclusion was unchanged (RR 3.31, 95% CI 2.45 to 4.47; 2 trials, 52,965 participants; I^2 = 43%).

Recall rate is the portion of participants recalled for repeat CT at 3 months and beyond 6 months for follow-up of a nodule or suspected lung cancer. Only two RCTs (Aberle 2011; Gohagan 2005) had baseline comparison data for recall rate (Analysis 5.3). The data suggested there were probably more recalls in the LDCT screening group compared to CXR groups (RR 5.31, 95% CI 1.73 to 16.34; 2 trials, 55,480 participants; I^2 = 99%) (analysis not shown). Heterogeneity was high between the groups. Both trials had no trial-wide algorithm, however had similar definitions for a positive screen. LSS (Gohagan 2005) was a feasibility study, and there were only two screening rounds, with participants advised to seek medical follow-up with specialists. Baseline screening recall rates from trials provided (Aberle 2011; Becker 2020; De Koning 2020; Field 2021; Gohagan 2005; Infante 2015; Paci 2017; Pastorino 2012; Wille 2016) are summarised in Table 3, with an overall recall rate following baseline screen of 18% (range of 5% to 23%). Of note, recall rates were defined differently between trials, with most trials including scans occurring up to 12 months postscreen and the NLST (Aberle 2011) and LSS (Gohagan 2005) data including all CT scans, not specifically recall scans, performed as a result of the baseline screen.

6) Smoking behaviour – cessation, relapse rates, smoking intensity

There were no common time points for assessment of quit rates. Individual trial results are presented in Analysis 6.1. Both the ITALUNG trial (Paci 2017) and the DLCST (Wille 2016) included smoking cessation as part of their programme, although Wille 2016 quantified it as minimal (< 5 minutes spent on smoking cessation per review). The ITALUNG (Paci 2017) trial and UKLS (Field 2021) confirmed smoking status via self-reporting only, whereas the DLSCT (Wille 2016) also confirmed smoking by measuring exhaled CO_2 levels.

- At 2 weeks post-randomisation, Field 2021 showed a higher quit rate in the LDCT screening group compared with control (RR 2.16, 95% CI 1.47 to 3.18; 1 trial, 1545 participants).
- At 1 year post-randomisation, there was probably no difference in quit rates between the groups in Wille 2016 (RR 1.08, 95% CI 0.88 to 1.32; 1 trial, 3124 participants).
- Within 2 years post-randomisation, Field 2021 again showed a higher quit rate in the LDCT screening group compared with control (RR 1.51, 95% CI 1.15 to 1.97; 1 trial, 1524 participants).
- At 4 years post-randomisation, Paci 2017 demonstrated there was possibly no difference in quit rates between the groups (RR 1.17, 95% CI 0.99 to 1.37; 1 trial, 2447 participants).

Only one trial presented smoking relapse rates in both groups (Wille 2016). There was probably no difference in relapse rates between the groups in this trial (RR 0.95, 95% CI 0.65 to 1.41; 1 trial, 888 participants; Analysis 6.2).

7) Health-related quality of life (HRQoL)/psychosocial consequences

HRQoL and psychosocial consequences were evaluated in four trials (Aberle 2011; De Koning 2020; Field 2021; Wille 2016). The trials measured different aspects of quality of life. Whilst small transient changes were at times reported, no long-term adverse consequences on HRQoL were reported. The DLSCT (Wille 2016) and UKLS (Field 2021) administered questionnaires to their whole trial cohort. The NLST (Aberle 2011) initially only invited participants of the LDCT screening group from 16 of the 23 American College of Radiology Imaging Network (ACRIN) sites with positive baseline LDCTs, however later they invited participants who had significant incidental findings (SIFs) on LDCT as well. The control group matched LDCT group participants with negative results with a total number of participants of 2812 for this outcome. The NELSON (De Koning 2020) trial also only included a portion of their cohort for this analysis, taking a random sample of 733 participants from each trial group (LDCT screening and control).

The following questionnaires were used as assessments in these trials.

- Lung cancer-specific questionnaire Consequences of Screening in Lung Cancer (COS-LC, Brodersen 2010): COS-LC consists of nine psychosocial scales: four core scales (24 core items) and five lung cancer screening-specific scales (25 lung cancer screening-specific items). The four core scales measure anxiety (7 items), behaviour (7 items), dejection (6 items), sleep (4 items) and smoking (2 items). Higher scores indicate more negative psychosocial consequences.
- Short form 36-item questionnaire (SF-36, Ware 1992) version 2: SF-36 has a physical component summary (PCS) and a mental component summary (MCS). The score ranges from 0-100. Higher scores indicate better HRQoL; lower scores indicate worse quality of life.
- Short form 12-item questionnaire (SF-12, Gandek 1998; Ware 1996) is a short version of the 36-item questionnaire which also has a PCS and a MCS, with both components having a maximum score of 50 each. As with the SF-36, higher scores indicated better HRQoL.
- EuroQol questionnaire (EQ-5D, Essink-Bot 1993; Kind 2005): EQ-5D is a health questionnaire with five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) as well as a visual analogue score (VAS). The VAS ranges from 0 (the worst imaginable health status) to 100 (the best imaginable health status).
- Spielberger State-Trait Anxiety Inventory (STAI-6) (van der Bij 2003): STAI-6 assesses generic anxiety, with scores ranging from 20 to 80; higher scores indicate more anxiety.
- Hospital Anxiety and Depression Scale (HADS): (Zigmond 1983): HADS consists of separate anxiety and depression components, each with a score ranging from 0 to 21. Scores for each component are considered normal (0-8), borderline abnormal (9-11) and abnormal (12-21).
- Impact of event scale (IES, Horowitz 1979): IES measures distress caused by traumatic events (in this instance lung cancer) and

consists of 15 items with total scores 0 to 75, with subscales for intrusion (0 to 35) and avoidance (0 to 40); higher scores indicated more distress.

- Revised 6-item Cancer Worry Scale (CWS-R): CWS-R has scores ranging from 4 to 24, with higher scores indicating more worry.

Lung cancer-specific questionnaires

DLSCT (Wille 2016) used COS-LC. Analysis 7.2 illustrates the change over time in mean differences (MDs) across all the core scales between the LDCT and control group at round two and five compared to baseline.

- Anxiety: at round two there was probably no difference between the groups (MD -0.13, 95% CI -0.33 to 0.07; 1 trial, 3352 participants), with higher anxiety scores in the control group compared with LDCT groups at round five (MD -0.51, 95% CI -0.76 to -0.26; 1 trial, 3185 participants).
- Behaviour: at round two both groups had increased negative response, with probably no difference between the groups (MD -0.21, 95% CI -0.42 to 0.00; 1 trial, 3337 participants). However, scores decreased in the LDCT group by round five (MD -0.60, 95% CI -0.88 to -0.32; 1 trial, 3180 participants).
- Dejection: at round two there was probably no difference between the groups, with elevated scores in both groups (MD -0.15, 95% CI -0.36 to 0.06; 1 trial, 3377 participants). However at round five, the LDCT group had fewer psychological consequences (MD -0.58, 95% CI -0.82 to -0.34; 1 trial, 3195 participants).
- Negative impact on sleep: at round two there was probably no difference between the groups, with elevated scores in both groups (MD -0.14, 95% CI -0.32 to 0.04; 1 trial, 3389 participants). However, at round five there was a significant difference favouring LDCT screening (MD -0.70, 95% CI -0.95 to -0.45; 1 trial, 3198 participants).
- Other domains (self-blame, focusing on airway symptoms, stigmatisation, introvert and harm of smoking): the lung cancer-specific scales tended to demonstrate more negative psychosocial consequences in the control group compared with the LDCT screening group from round two to round five.

Anxiety

When we combined standardised mean difference (SMD) in anxiety scores for the three available trials (De Koning 2020; Field 2021; Wille 2016; Analysis 7.1), the evidence favoured lower anxiety scores in the LDCT screening group (SMD -0.43, 95% CI -0.59 to -0.27; 3 trials, 8153 participants; I^2 = 0%; low-certainty evidence), although scores were not necessarily abnormal in either group.

- In the NELSON trial (De Koning 2020), there was probably no difference between the groups at baseline (MD -0.48, 95% CI -1.63 to 0.67; 1 trial, 1288 participants) and at 2 years (MD -0.75, 95% CI -1.99 to 0.49; 1 trial, 931 participants).
- In the UKLS trial (Field 2021), HADS anxiety scores were in the normal range in both groups, however scores were lower in the LDCT group compared with the control groups at baseline (MD -0.07, 95% CI -0.11 to -0.03; 1 trial, 4037 participants) and at 10 months to 27 months (MD -0.36, 95% CI -0.57 to -0.15; 1 trial, 4037 participants).
- We did not include the NLST trial (Aberle 2011) in this analysis as the control group consisted of participants with negative screen results and not participants from the CXR group. Participants were separated based on screening outcome (negative, true positive, false positive, and SIFs) (Analysis 7.5). There was no difference in anxiety levels between the groups for the participants with negative screens at baseline (MD -0.26, 95% CI -1.79 to 1.27; 1 trial, 1162 participants) and at 6 months (MD -0.33, 95% CI -1.91 to 1.25; 1 trial, 1019 participants). There was probably no difference between the groups with participants with true positive screens at baseline (MD 1.63, 95% CI -6.31 to 9.57; 1 trial, 48 participants) and at 6 months (MD -2.69, 95% CI -11.69 to 6.31; 1 trial, 42 participants). False-positive participants also did not demonstrate a difference in anxiety levels at baseline (MD 1.77, 95% CI -0.04 to 3.58; 1 trial, 835 participants) or at 6 months (MD 1.31, 95% CI -0.61 to 3.23; 1 trial, 703 participants) between the groups.

Depression

The UKLS trial (Field 2021) used the HADS score for depression. These scores were within normal limits for both groups. The LDCT group reported lower scores compared with the control group at baseline (MD -0.06, 95% CI -0.10 to -0.02; 1 trial, 4037 participants) and at 10 months to 27 months (MD -0.24, 95% CI -0.40 to -0.08; 1 trial, 4037 participants).

Stress

Both the NESLON trial (De Koning 2020) and UKLS (Field 2021) measured stress using different instruments.

- The NELSON trial (De Koning 2020) used the IES score. There was probably no difference between the groups at baseline (MD 0.03, 95% CI -0.88 to 0.94; 1 trial, 1288 participants) and at 2 years (MD -0.31, 95% CI -1.30 to 0.68; 1 trial, 931 participants). However, they reported that people in the LDCT group who had indeterminate results had elevated distress following the result at 2 months.
- The UKLS trial (Field 2021) used the CWS-R and did not report any difference between groups in cancer distress at 10 months to 27 months. However, they did observe that those participants referred to the lung cancer multidisciplinary meeting reported more lung cancer distress in the short term (approximately 2 weeks after randomisation to the non-screening arm or receiving results of the baseline LDCT) (mean score 11.88, 95% CI 11.10 to 12.72), although were more satisfied with their participation in the trial.

Generic HRQoL

The NELSON trial (De Koning 2020) measured HRQoL using the SF-12 questionnaire and EQ-5D, whilst NLST (Aberle 2011) used the SF-36 version.

- In the NELSON trial (De Koning 2020), there was probably no difference in the SF-12 scores between the groups for both the PCS and MCS components, both at baseline and 2 years. There was also probably no difference between the two groups with EQ-5D VAS at baseline and 2 years.
  - PCS baseline (MD 0.28, 95% CI -0.66 to 1.22; 1 trial, 1288 participants) and at 2 years (MD 0.88, 95% CI -0.34 to 2.10; 1 trial, 931 participants).
  - MCS baseline (MD -0.06, 95% CI -1.42 to 1.30; 1 trial, 1288 participants) and at 2 years (MD 0.81, 95% CI -0.65 to 2.27; 1 trial, 931 participants).

- EQ-5D VAS baseline (MD 0.69, 95% CI -0.98 to 2.36; 1 trial, 1288 participants) and at 2 years (MD 2.08, 95% CI 0.18 to 3.98; 1 trial, 1010 participants).

- In the NLST trial (Aberle 2011), groups were divided again by results of screening (negative, true positive, false positive, and SIF).
  - Participants with true-positive screens did have lower PCS and MCS scores (Analysis 7.3; Analysis 7.4), which declined at 6 months, however scores were probably not significantly different between groups.
    - PCS at baseline (MD -1.94, 95% CI -7.33 to 3.45; 1 trial, 63 participants) and at 6 months (MD -0.20, 95% CI -7.32 to 6.92; 1 trial, 42 participants). MCS at baseline (MD -1.74, 95% CI -6.66 to 3.18; 1 trial, 63 participants) at 6 months (MD 0.08, 95% CI -8.19 to 8.35; 1 trial, 42 participants).
  - There was probably no significant difference between the groups for those with negative and false-positive screens at baseline and 6 months.
    - Participants with a negative screen: PCS at baseline (MD -1.07, 95% CI -2.09 to -0.05; 1 trial, 1381 participants) and at 6 months (MD -0.11, 95% CI -1.38 to 1.16; 1 trial, 1019 participants). MCS at baseline (MD -0.85, 95% CI -1.97 to 0.27; 1 trial, 1381 participants) and at 6 months (MD -0.15, 95% CI -1.52 to 1.22; 1 trial, 1019 participants).
    - Participants with false-positive screens: PCS at baseline (MD -0.72, 95% CI -1.98 to 0.54; 1 trial, 1024 participants) and at 6 months (MD -0.78, 95% CI -2.42 to 0.86; 1 trial, 703 participants). MCS at baseline (MD -0.19, 95% CI -1.43 to 1.05; 1 trial, 1024 participants) and at 6 months (MD -1.02, 95% CI -2.67 to 0.63; 1 trial, 703 participants).

8) Cancer stage at diagnosis

We grouped trial results by time points (Analysis 8.1; Analysis 8.2; Analysis 8.3; Analysis 8.4; Analysis 8.5). Where specified in the trials, we separated limited and extensive small cell lung cancer (SCLC) from TNM (tumour, node, metastasis) staging (Goldstraw 2016).

- At baseline: we included five trials (Aberle 2011; Blanchon 2007; Gohagan 2005; Infante 2015; Wille 2016; Analysis 8.1). The evidence suggested that stage 1 lung cancer was detected more in the LDCT screening group (RR 2.41, 95% CI 1.86 to 3.12; 5 trials, 64,092 participants; I^2 = 0%). Analysis showed there was possibly no difference between the groups for stage 2 lung cancer (RR 1.88, 95% CI 0.99 to 3.58; 5 trials, 64,092 participants; I^2 = 0%). There were fewer stage 3 cases of lung cancer in the control group, however heterogeneity between trials was high (RR 4.28, 95% CI 1.06 to 17.27; 5 trials, 64,092 participants; I^2 = 59%). Heterogeneity was reduced to zero when we removed Aberle 2011, although the outcome was unchanged (RR 8.69, 95% CI 2.33 to 32.35; 4 trials, 10,637 participants; I^2 = 0%). There was probably no difference between the groups with stage 4 cancer (RR 1.05, 95% CI 0.70 to 1.55; 5 trials, 64,092 participants; I^2 = 0%) and unknown stage lung cancer (RR 0.99, 95% CI 0.31 to 3.13; 2 trials, 56,773 participants; I^2 = 0%). The DLSCT (Wille 2016) was the only trial that reported limited and extensive stages. There were no cases in limited stage, and the extensive stage had more cases in the screening group. In the LDCT screening group, 53% of diagnosed lung cancers were stage 1, 7% of diagnosed lung cancers were stage 2, 23% of diagnosed lung cancers were stage 3, and 14% of diagnosed lung cancers were stage 4. In the control group, 40%, 7%, 28%, and 23% of diagnosed cancers, respectively were stages 1, 2, 3, and 4.
- At 1 year: we included three RCTS (Aberle 2011; Gohagan 2005; Wille 2016; Analysis 8.2). The evidence suggested that stage 1 cancer was detected more in the LDCT compared with the control group (RR 2.57, 95% CI 1.24 to 5.32; 3 trials, 60,877 participants; I^2 = 16%). There was probably no difference between the groups for stages 2 (RR 1.39, 95% CI 0.68 to 2.84; 3 trials, 60,877 participants; I^2 = 0%) and 3 lung cancer (RR 1.22, 95% CI 0.76 to 1.95; 3 trials, 60,877 participants; I^2 = 0%). The evidence showed that stage 4 lung cancer was detected more in the control group than in the LDCT screening group (RR 0.48, 95% CI 0.30 to 0.77; 3 trials, 60,877 participants; I^2 = 0%). The NLST (Aberle 2011) was weighted 96% in that analysis. There was no difference between the groups for limited (RR 1.00, 95% CI 0.06 to 15.98; 1 trial, 4104 participants; I^2 = 0%) and extensive (RR 3.00, 95% CI 0.12 to 73.60; 1 trial, 4104 participants; I^2 = 0%) stages of lung cancer, as well as unknown stage (RR 1.35, 95% CI 0.17 to 10.75; 2 trials, 56,773 participants; I^2 = 17%). In the LDCT screening group, 57% of diagnosed lung cancers were stage 1, 9% of diagnosed lung cancers were stage 2, 19% of diagnosed lung cancers were stage 3, and 13% of diagnosed lung cancers were stage 4. In the control group, 30%, 9%, 22%, and 37% of diagnosed cancers respectively, were stages 1, 2, 3, and 4.
- At 2 years: we included two RCTS (Aberle 2011; Wille 2016; Analysis 8.3). The evidence suggested that stage 1 cancer was detected more in the LDCT group compared with control screening group (RR 3.53, 95% CI 1.66 to 7.53; 2 trials, 57,559 participants; I^2 = 20%). There was probably no difference between the groups for stages 2, 3, and 4 lung cancer (RR 1.08, 95% CI 0.49 to 2.37; 2 trials, 57,559 participants; I^2 = 0%), (RR 0.92, 95% CI 0.59 to 1.44; 2 trials, 57,559 participants; I^2 = 0%) and (RR 0.80, 95% CI 0.52 to 1.24; 2 trials, 57,559 participants; I^2 = 0%), respectively. The DLSCT trial (Wille 2016) did not have any events in stage 2 lung cancer. We only included one trial (Wille 2016) for each of extensive (RR 0.14, 95% CI 0.01 to 2.76; 1 trial, 4104 participants) and unknown stages (RR 7.00, 95% CI 0.86 to 56.91; 1 trial, 53,455 participants) with no limited cases. In the LDCT screening group, 63% of diagnosed lung cancers were stage 1, 5% of diagnosed lung cancers were stage 2, 14% of diagnosed lung cancers were stage 3, and 15% of diagnosed lung cancers were stage 4. In the control group, 33%, 8%, 26%, and 31% of diagnosed cancers respectively, were stages 1, 2, 3, and 4.
- 5 to < 10 years post-randomisation: we included four trials (Becker 2020; Field 2021; Infante 2015; Paci 2017; Analysis 8.4). All trials used TNM staging. The NLST trial (Aberle 2011) also included an occult lung cancer stage, which we combined with stage 1 for this analysis. The evidence showed that stage 1 occurred more frequently in the LDCT screening group (RR 2.26, 95% CI 1.43 to 3.57; 4 trials, 13,676 participants; I^2 = 0%). There was probably no difference between the groups for stages 2 (RR 0.78, 95% CI 0.37 to 1.66; 4 trials, 13,676 participants; I^2 = 9%) and 3 lung cancer (RR 0.84, 95% CI 0.47 to 1.49; 4 trials, 13,676 participants; I^2 = 27%). Heterogeneity was mild amongst the trials for stage 3. The evidence suggested fewer cases of stage 4 lung cancer detected in the LDCT screening group (RR 0.55, 95% CI 0.34 to 0.91; 4 trials, 13,676 participants; I^2 = 57%). Heterogeneity was present and removing Field 2021 resulted in no heterogeneity without changing the findings (RR 0.70, 95%

CI 0.50 to 0.97; 3 trials, 9708 participants; I^2 = 0%). There was probably no difference between the groups with lung cancer of unknown stage (RR 0.67, 95% CI 0.41 to 1.12; 4 trials, 13,676 participants; I^2 = 5%). In the LDCT screening group, 31% of diagnosed lung cancers were stage 1, 7% of diagnosed lung cancers were stage 2, 17% of diagnosed lung cancers were stage 3, and 32% of diagnosed lung cancers were stage 4. In the control group, 11%, 8%, 16%, and 46% of diagnosed cancers respectively were stages 1, 2, 3, and 4.

- ≥ 10 years post-randomisation: we included four trials (Aberle 2011; Paci 2017; Pastorino 2012; Wille 2016; Analysis 8.5). As previously, we combined occult lung cancer with stage 1 lung cancer for Aberle 2011. The evidence showed that stage 1 was detected more frequently in the LDCT screening group (RR 3.28, 95% CI 1.82 to 5.90; 4 trials, 11,409 participants; I^2 = 56%). The heterogeneity level was acceptable. There was probably no difference between the groups for stages 2 (RR 0.94, 95% CI 0.76 to 1.17; 4 trials, 64,864 participants; I^2 = 0%) and stage 3 lung cancer (RR 1.23, 95% CI 0.79 to 1.93; 4 trials, 64,864 participants; I^2 = 56%). The heterogeneity level was acceptable amongst the trials for stage 3 lung cancer. The evidence suggested there were fewer cases of stage 4 lung cancer in the LDCT screening group (RR 0.77, 95% CI 0.69 to 0.86; 4 trials, 64,864 participants; I^2 = 0%) There were possibly fewer cancers at unknown stages in the LDCT group compared with the control group (RR 0.67, 95% CI 0.45 to 0.99; 3 trials, 60,765 participants; I^2 = 24%). In the LDCT screening group, 40% of diagnosed lung cancers were stage 1, 8% of diagnosed lung cancers were stage 2, 18% of diagnosed lung cancers were stage 3, and 28% of diagnosed lung cancers were stage 4. In the control group, 26%, 9%, 18%, and 37% respectively, were stages 1, 2, 3, and 4.

9) Histology

We grouped trial results by time points (Analysis 9.1; Analysis 9.2; Analysis 9.3). For the purposes of this review, histological types presented are small cell lung carcinoma (SCLC), mixed SCLC and non-small cell lung carcinoma (NSCLC), squamous cell carcinoma (SCC), adenocarcinoma (AC), bronchioalveolar carcinoma (BAC), and other. The category of 'other' is all other histological subtypes presented in trials, including sarcomatoid carcinomas, large cell carcinomas, neuroendocrine tumours and neuroendocrine carcinomas. It should be noted that BAC was reclassified as various adenocarcinoma subtypes in the lung cancer TNM classification by the World Health Organization (WHO) (Nicholson 2022), however has been included here as presented by the relevant trials.

- Baseline: we included four trials (Aberle 2011; Blanchon 2007; Gohagan 2005; Infante 2015; Analysis 9.1). There was probably no difference in the number of SCLC and other histology between groups (RR 0.84, 95% CI 0.45 to 1.57; 4 trials, 59,987 participants; I^2 = 2%) and (RR 1.32, 95% CI 0.90 to 1.94; 4 trials, 59,987 participants; I^2 = 0%), respectively. SCC, AC, and BAC were more common in the LDCT arm (RR 1.47, 95% CI 1.01 to 2.13; 4 trials, 59,987 participants; I^2 = 0%), (RR 2.81, 95% CI 1.38 to 5.71; 4 trials, 59,987 participants; I^2 = 46%) and (RR 4.94, 95% CI 2.41 to 10.10; 2 trials, 55,904 participants; I^2 = 0%), respectively. Heterogeneity between groups was moderate in the AC analysis.
- 1 year: we only included one trial (Gohagan 2005; Analysis 9.2), with more cases of AC found in the LDCT screening groups and probably no difference between groups for SCLC (RR 2.00, 95% CI 0.37 to 10.89; 1 trial, 3318 participants), SCC (RR 0.83, 95% CI 0.25 to 2.72; 1 trial, 3318 participants), AC (RR 2.66, 95% CI 1.24 to 5.71; 1 trial, 3318 participants) and other histology (RR1 2.33, 95% CI 0.60 to 9.00; 1 trial, 3318 participants).
- ≥ 7 years post-randomisation: we included seven RCTS in the analysis (Aberle 2011; Becker 2020; Field 2021; Infante 2015; Paci 2017; Pastorino 2012; Wille 2016; Analysis 9.3). The latest available time point was 11.3 years post-randomisation (Aberle 2011). For the DLCST trial (Wille 2016), the adenocarcinoma category also included mixed AC and BAC, as well as mixed AC and SCC. The MILD trial (Pastorino 2012) had both annual and biennial arms combined in the intervention group. For consistency, the latest available time point for data was taken for each trial. In the LUSI trial (Becker 2020), this meant that only data pertaining to three categories (AC, BAC, and other) were included. For SCLC, SCC, and other, there was probably no difference between the groups, with moderate heterogeneity between the trials for the other category: SCLC (RR 0.86, 95% CI 0.74 to 1.01; 6 trials, 71,281 participants; I^2 = 0%), SCC (RR 1.04, 95% CI 0.81 to 1.32; 6 trials, 71,281 participants; I^2 = 26%) and other (RR 0.87, 95% CI 0.68 to 1.11; 7 trials, 75,333 participants; I^2 = 40%). The evidence suggested that AC and BAC were more common in the LDCT screening group, with high heterogeneity between trials in the AC category: AC (RR 1.49, 95% CI 1.05 to 2.10; 7 trials, 75,333 participants; I^2 = 82%) (analysis not shown) and BAC (RR 2.73, 95% CI 1.96 to 3.81; 3 trials, 61,610 participants; I^2 = 0%). When we removed NLST (Aberle 2011) from the AC analysis, heterogeneity decreased (RR 1.62, 95% CI 1.13 to 2.34; 6 trials, 21,879 participants; I^2 = 69%). NLST (Aberle 2011) was the only included trial in this analysis that used CXR screening as a comparator. Mixed SCLC and NSCLC was only reported in one trial (Wille 2016) (RR 0.14, 95% CI 0.01 to 2.76; 1 trial; 4104 participants).

10) Other outcomes

- Biomarkers: two trials have published data on small samples of their trial population DNA and microRNA profiles (Paci 2017; Pastorino 2012). Becker 2020 published early data on autoantibodies to tumour-associated antigens in a subgroup of their cohort.
- Response rate: eight RCTs had available data (Becker 2020; Blanchon 2007; De Koning 2020; Field 2021; Gohagan 2005; LaRocca 2002; Paci 2017; Wille 2016), which is summarised in Table 4. In larger trials that used information mail outs (Becker 2020; De Koning 2020; Field 2021; Gohagan 2005; Paci 2017), only ≤ 5% of those contacted, enrolled in the trial.
- Adherence to screening: eight RCTs reported adherence to screening (Aberle 2011; Becker 2020; Blanchon 2007; De Koning 2020; Field 2021; Gohagan 2005; Paci 2017; Pastorino 2012). Overall, adherence to screening was good, with a decline noted at and after 5 years (Table 4). Three RCTs had comparative data with CXR control groups (Aberle 2011; Blanchon 2007; Gohagan 2005). Heterogeneity was high between the groups, however the evidence suggested poorer adherence in the LDCT screening group (RR 1.05, 95% CI 1.01 to 1.09; 3 trials, 57,539 participants; I^2 = 85%) (analysis not shown).
- Contamination: seven RCTS reported on contamination (Becker 2020; Blanchon 2007; De Koning 2020; Gohagan 2005; Infante 2015; Pastorino 2012; Wille 2016). In LUSI (Becker 2020), 13% of the control group had undergone a CT scan. In DESPICAN

(Blanchon 2007), 6 participants had inadvertently undergone LDCT. In the NESLON trial (De Koning 2020) 4% of the control group in a random sample of 1460 participants had undergone chest CT. One per cent of control arm participants underwent a LDCT in the MILD trial (Pastorino 2012), and three participants in the DLCST control group (Wille 2016) had a chest CT for lung cancer screening purposes. Neither LSS (Gohagan 2005) nor DANTE (Infante 2015) clearly differentiated the number of scans performed for screening purposes only. Reported contamination rates are detailed in Table 4. Three RCTs had comparative data with control arms (Gohagan 2005; Infante 2015; Wille 2016). The evidence suggested there was no significance difference between the groups, however heterogeneity was high (RR 1.35, 95% CI 0.32 to 5.68; 3 trials, 6902 participants; I^2 = 74%).

- Interval lung cancers: seven trials reported rates of interval cancers at different time points (Aberle 2011; Becker 2020; De Koning 2020; Gohagan 2005; Paci 2017; Pastorino 2012; Wille 2016). These are summarised in Table 5.
- False negatives: five trials reported false-negative cases at various time points (Aberle 2011; De Koning 2020; Field 2021; Infante 2015; Pastorino 2012). In NLST (Aberle 2011), there were < 1% false negatives each round of screening for the LDCT screening group and CXR control group for the first 3 years, with more false-negative results in the CXR screening compared with LDCT screening (Analysis 5.2). The NELSON trial (De Koning 2020) also reported small numbers of false negatives with a total of five, seven, and seven false negatives across the first, second and third round of screening, respectively. The UKLS trial (Field 2021) reported three false negatives from their baseline LDCT. The DANTE trial (Infante 2015) reported one false negative in the intervention arm. The MILD trial (Pastorino 2012) reported 17 false negatives in the annual LDCT group and nine in the biennial LDCT group.
- Incidental findings: six trials reported rates of incidental findings (Aberle 2011; Blanchon 2007; De Koning 2020; Field 2021; Infante 2015; Wille 2016), and these are summarised in Table 5.
- Cost: three trials reported cost data (Aberle 2011; Field 2021; Wille 2016). The lowest cost was in the UK trial (Field 2021) which, following clarification with authors, was GBP 186 per screen/per participant, including costs of recruitment. In the Danish trial (Wille 2016), the cost of a LDCT screen was EUR 282, with the total cost per year of healthcare costs per participant being EUR 3756 in the screening group. Of note, the control arm cost per participant per year in this trial was EUR 3474 (EUR 2348 without lung function or counselling). The USA trial (Aberle 2011) had a cost per participant in the LDCT screening group of USD 1130, compared with USD 336 for the CXR participant. The costs of screening included the cost of investigating clinically SIFs.
- Use of anxiolytics and antidepressants: only one trial investigated this outcome and concluded that participation in the trial was not associated with a change in prescriptions of these medications (Wille 2016).
- Feasibility of general practitioner (GP) enrolment to lung cancer screening trial: one trial reported this as an outcome (Blanchon 2007), with participation rate of GPs reported as 41%.

DISCUSSION

Summary of main results

Primary outcomes

- For lung cancer-related mortality, moderate-certainty evidence showed a difference favouring LDCT screening. When we only included high-certainty trials, the evidence still favoured LDCT screening.
- The evidence showed that the number of invasive and non-invasive interventions is higher in the LDCT screening group compared with the control group, including rates of invasive interventions for non-lung cancer-related disease. However, there was probably no difference in death postsurgery between groups.

Secondary outcomes

- For all-cause mortality, the evidence showed a small difference favouring screening with LDCT. The analysis still favoured screening with LDCT when only high-certainty trials were included.
- For estimated overdiagnosis at 10 or more years, the combined risk was 18%. However, the 95% CI was wide, suggesting possibly no difference between the groups, with a lower limit of the 95% CI just below 0 and an upper limit of 36%. This is in keeping with the incidence of lung cancer, demonstrating that there was possibly no difference in incidence between LDCT screening and control groups at 10 or more years.
- For false-positive results from scans, the evidence showed that these were higher in the LDCT screening group.
- For recall rates, the evidence showed that these were higher in the LDCT screening group.
- For smoking cessation rates, results were mixed. However, there was probably no significant difference in smoking relapse rates between LDCT screening and control groups.
- For psychosocial consequences, the evidence was of low certainty due to inconsistencies in outcome measures, sample groups, and timing of assessments. Overall the limited evidence available did not suggest any long-term adverse impact on psychosocial well-being or HRQoL with LDCT screening.
- For lung cancer staging, the evidence showed there was more stage 1 lung cancer detected in the LDCT group compared with control, across the time points. As time from randomisation increased, there was probably no difference between groups for stage 2 and 3 lung cancer. In later time points, the evidence showed there was more stage 4 lung cancer in the control groups compared to LDCT screening group.
- For lung cancer histology, the evidence showed there was more squamous cell carcinoma (SCC), adenocarcinoma (AC) and bronchioalveolar carcinoma (BAC) detected in the LDCT screening group compared with control groups at baseline. AC and BAC remained more prevalent in the LDCT screening group at later time points.

Overall completeness and applicability of evidence

We identified 11 eligible RCTs and included eight for the main meta-analysis of the primary outcome, lung cancer-related mortality; we could not include two trials in the meta-analysis due to data being unavailable, and we excluded one trial (Gohagan 2005)

from Analysis 1.1 as it did not have any planned follow-up time points.

The following considerations may affect the strength and completeness of the conclusions of this review.

- Participant characteristics
  - Participants enrolled in these trials tended to have a strong tobacco smoking exposure history as a result of trial inclusion criteria. Trials investigating the role of LDCT for lung cancer-screening in non-smoking populations are still ongoing (Ongoing studies). Only one trial used a validated tool to predict lung cancer risk, with the other trials using smoking exposure as part of the inclusion criteria.
  - Two RCTs had either zero or a significantly underrepresented number of female participants (De Koning 2020; Infante 2015). This is significant, as the subgroup analysis of female participants demonstrated a larger lung cancer-related mortality benefit with LDCT screening compared to the male participants (Analysis 1.8), although CIs did overlap.
  - All included trials were conducted in the USA or Europe. Whilst not all trials reported breakdown of ethnicity or race, the two trials that did, reported a significant majority of white participants compared to other races (Aberle 2011; Field 2021).
  - Seven trials had additional fitness requirements (Becker 2020; Blanchon 2007; De Koning 2020; Infante 2015; Paci 2017; Pastorino 2012; Wille 2016), including fitness for surgery for entry into the trial.
  - Information regarding education level and socioeconomic status of participants was limited. Three trials described education levels amongst participants (Aberle 2011; Field 2021; Wille 2016), with 32% of NLST having a tertiary degree or higher (Aberle 2011).
- We could not provide enough information about the potential harms of LDCT screening as only a few trials provided data from all trial groups (Aberle 2011; Gohagan 2005; Infante 2015; Pastorino 2012). Heterogeneity ranged from high to low amongst trials in these analyses, as trials did not have uniform reporting and categorisation of invasive and non-invasive interventions. Additionally, trials did not have a consensus definition for significance of nodules and investigation pathways.
- Included trials did not use consistent measures of HRQoL, which made comparison challenging.
  - Only two trials administered the questionnaires to their whole cohort (Field 2021; Wille 2016), with the NLST (Aberle 2011) and the NESLON (De Koning 2020) trials inviting only a small portion of their cohort. The NLST trial limited their assessment to only those in the LDCT screening group (Aberle 2011).
  - Whilst the exact timing of assessments varied, all trials consistently reported no long-term adverse consequences of screening with LDCT, except for true positives (participants diagnosed with cancer as a result of screening) in NLST (Aberle 2011). The NLST trial reported lower HRQoL and more anxiety in this group.
  - The NELSON trial had an indeterminate category for classification of nodules (De Koning 2020), and reported an elevated cancer-specific distress core in this group at 2 months. There was no difference between groups at 2 years.
  - The UKLS trial reported less decision satisfaction for participants in the control arm (Field 2021), which may reflect an increased awareness of risk of lung cancer in the control arm without the ability to participate in screening. Anxiety and lung cancer-related distress were higher in the group referred to multidisciplinary meetings postscreening, however this group had high satisfaction rates in their decision to participate in screening.
  - The DLCST reported more negative responses in both the screening and no-screening groups in the fields of behaviour, dejection and negative impact on sleep at earlier time points (Wille 2016), however the impact decreased by round five of screening. They also noted less anxiety in the screening at round five. Their response rate to questionnaires in the control group was lower (76% compared with 94% in the LDCT screening group). In their smaller cohort study, Wille 2016 reported that participants with false-positive results had more negative psychosocial consequences of screening compared with those in the control group (no screening) or true negatives in the short term, with no significant long-term consequences.
  - The DLSCT also reviewed psychosocial status and demographics of participants in the control group who did not attend their annual clinical review (Wille 2016). The trial reported that non-attenders to visits were from more disadvantaged sociodemographic backgrounds and had lower psychosocial questionnaire scores from preceding rounds. This is an important consideration for lung cancer screening, adding to the need for more comprehensive assessments of psychosocial well-being of potential lung cancer screening participants and acknowledging that the population who participates and engages in a trial may not be reflective of the general population.
  - Further research is required to assess factors affecting engagement in screening and adherence and how to manage potential short-term adverse psychosocial outcomes.
- Effect of screening on smoking was also limited due to available data.
  - Five trials involved smoking cessation counselling (Becker 2020; De Koning 2020; Paci 2017; Pastorino 2012; Wille 2016).
  - Motivation to quit was reported in two trials (De Koning 2020; Wille 2016), however they did not provide comparative data for trial arms.
- The definition of recall rates was not consistent across all trials (Aberle 2011; Becker 2020; De Koning 2020; Field 2021; Gohagan 2005; Infante 2015; Paci 2017; Pastorino 2012; Wille 2016). Recall rates in LUSI included all early recalls up to 12 months following LDCT (Becker 2020), whereas in the MILD trial it was defined as 3 months post-LDCT scan (Pastorino 2012). The NLST reported all further chest CT, and did not specify recall CTs only (Aberle 2011). The NELSON trial also had an intermediate category for abnormal results (De Koning 2020), which likely resulted in an under appreciation of false-positive screens, when defined as any result that is not a negative screen.
- Incidental findings were also not well described across the included trials, with varying categories of findings reported. Incidental findings are likely common however, with the NLST reporting 15% of participants had incidental cardiovascular disease noted on baseline LDCT (N =17,309 from non-ACRIN centres; Aberle 2011).

- Some trials had limited publications. All RCT authors were contacted by a reviewer (DM) where required.

Quality of the included trials

Included trials were generally well-designed, and all included trials were RCTs.

- Due to the nature of the intervention, an open-label design may have increased performance bias in subjective outcomes.
- Only a few trials used blinded death panels to review lung cancer-related mortality, which may have influenced detection bias.
  - Six of the included trials used a death review panel in some capacity (Aberle 2011; Becker 2020; De Koning 2020; Infante 2015; Paci 2017; Wille 2016), particularly when assessing lung cancer-related deaths for part or all of the duration of the trial.
  - Three trials used registries and/or death certificates only to determine cause of death (Field 2021; Gohagan 2005; Pastorino 2012).
  - The NELSON trial reviewed the use of death review panels to determine cause of death compared with death certificates in the first 266 Netherlands cohort deaths (De Koning 2020); the use of the review panel reclassified 12% of cases. The NELSON trial subsequently ceased using a death review panel thereafter.
  - The NLST trial also reviewed use of a death review panel compared with death certificates to accurately determine cause of death (Aberle 2011). Cause of death was reclassified in 3% of cases following review by panel, with death certificates having a sensitivity of 91% for cause of death. The authors then revisited analysis of lung cancer-related mortality using lung cancer-related deaths provided by death certificate, and found a lung cancer mortality reduction of 18% (95% CI 4.2 to 25) compared to the 20% (95% CI 6.7 to 26.7) published.
  - The use of death panels in trials is expensive, and further research is required to determine whether it significantly adds to the assessment of lung cancer-related mortality.
  - The use of registries alone for follow-up and detection of mortality and lung cancer incidence was a concern, as it was limited by trial access to participant data, delays from outcome to registry notification, and assumed participants had remained in the catchment of the registry without name change or errors. In the NLST's extended follow-up for instance (Aberle 2011), not all home state registries participated in the linkage, and some screening centres did not have access to participants' details to complete the linkage. The LUSI trial also had limitations with registry linkage (Becker 2020), with 39 participants declining data access. The UKLS trial had participants who had not consented to data linkages or had opted out of national registries (Field 2021).
  - Given concerns regarding completeness of follow-up data, this review prioritised planned and/or active follow-up in analysis over unplanned extended follow-up, as this tended to rely more on registry data and some trials which had used the death panel (Aberle 2011; Paci 2017), ceased after planned follow-up.
- All-cause mortality results were reliable across included trials.
- Regarding risk of bias, excluding those with unclear risk (Becker 2020; Blanchon 2007; LaRocca 2002), overall most domains of importance were low risk. There were a few trials that did have high risk for certain domains (De Koning 2020; Field 2021; Gohagan 2005; Infante 2015; Pastorino 2012), however this is unlikely to have had a significant impact on the results presented.

Certainty of the evidence

See Summary of findings 1.

We graded lung cancer-related mortality as having moderate-certainty evidence as it included eight trials which had low to high risk of bias. It should be noted that one trial had CXR as a comparison rather than no screening (Aberle 2011). Whilst screening with CXR has not been shown to reduce lung cancer-related mortality (Manser 2013), there may potentially be some impact from screening with CXR, which may have diluted the effect of LDCT screening in the NLST trial. However, there was no heterogeneity between the included trials. The included trials also had different definitions for positive scans (Aberle 2011; Becker 2020; De Koning 2020; Field 2021; Infante 2015; Paci 2017; Pastorino 2012; Wille 2016).

We graded all-cause mortality as having moderate-certainty evidence as the eight included trials had risk of bias ratings from low to high (Aberle 2011; Becker 2020; De Koning 2020; Field 2021; Infante 2015; Paci 2017; Pastorino 2012; Wille 2016). The difference was small, with only a 5% risk reduction with screening and a 95% CI upper limit of 0.99 (1% risk reduction). CXR as a comparator in the NLST may have impacted the effect (Aberle 2011).

We graded overdiagnosis as having low-certainty evidence due to risk of bias in the included trials and high heterogeneity between trials. The heterogeneity was largely due to the DLCST (Wille 2016), which had significantly higher lung cancer incidence in the LDCT screening group compared with no screening. There was a higher incidence of lung cancer diagnosed postcessation of screening in the screening group, which was unusual and not adequately explained by the mild overrepresentation of smoking history > 35 pack years and lower forced expiratory ratio (FER) in the screening group at baseline. We chose to present the follow-up data at 10 or more years despite this rating as it probably provides a better estimate for overdiagnosis of lung cancer with LDCT screening. Except for the DLSCT (Wille 2016), the other trials demonstrated a reduction in estimated overdiagnosis as time from randomisation increased. The other consideration which was not well explored in all trials was the background rates of CT scans in each country for other purposes, which may conversely diminish the perceived impact of overdiagnosis.

We graded the outcomes 'number of invasive tests' and 'any death postsurgery' as having moderate-certainty evidence as both analyses included trials with concerns regarding risk of bias.

We graded HRQoL and psychosocial consequences as having low-certainty evidence because we judged two of the three trials contributing to this outcome at high risk of bias and the included trials were different in their assessment of this outcome (De Koning 2020; Field 2021; Wille 2016), and this limited our ability to combine results. Only two trials included the whole trial cohort in their quality of life assessments (Field 2021; Wille 2016). The UKLS

trial administered the questionnaires to the whole cohort (Field 2021). The DLCST also administered their questionnaires to the whole cohort (Wille 2016), however performed an additional nested cohort trial focusing on those with a positive screen result. The NESLON trial took a random sample of 733 participants from each trial group (LDCT screening and control) (De Koning 2020). In the NLST (Aberle 2011), which we excluded from the meta-analysis as it did not have data from the CXR group, only 16 sites invited participants to complete questionnaires. Of those 16 sites, only those with a positive scan were initially invited to participate, with the NLST subsequently inviting participants with a negative scan but SIFs on LDCT at a later time point. This cohort of participants was then matched with controls who had a negative LDCT scan. The tools used for assessment of this outcome also varied, with only one trial using a lung cancer-specific tool to assess psychosocial consequences (Wille 2016). The NELSON trial (De Koning 2020) and UKLS trial (Field 2021) used lung cancer-specific distress scores. The NLST (Aberle 2011) and NELSON trial (De Koning 2020) both used generic health questionnaires (Short Form-12 and 36), as well as the STAI-6 for anxiety. The UKLS trial also measured Hospital Anxiety and Depression Scale (HADS), Cancer Worry Scale, and used a satisfaction with decision score (Field 2021). The trials also did not evaluate outcomes at uniform time points. The NLST assessed before the scan (could be any screen interval), 1-month postscreen, and 6 months postscreen (Aberle 2011). The NELSON trial assessed at baseline, 2 months post-randomisation, and at 2 years (prior to the third screen) (De Koning 2020). The UKLS trial collected questionnaires before randomisation, at 2 weeks (after participants had received results of screen or been notified of allocation to control arm), and at 10 months to 27 months (Field 2021). The DLCST administered questionnaires annually for five years (Wille 2016). Their nested cohort trial collected questionnaires at baseline, 1 week (postresult of screen or annual visit), 1 month, 6 months, and 18 months. The DLSCT also reviewed psychosocial status and demographics of participants in the control group who did not attend their annual clinical review. The trial reported that non-attenders to visits were from socioeconomically disadvantaged backgrounds and had lower psychosocial questionnaire scores from preceding rounds. This is an important consideration for lung cancer screening, as lung cancer is disproportionally represented in this group (Mao 2001).

Potential biases in the review process

This review used the Cochrane highly-sensitive search strategy and aimed to include all trials, both published and unpublished, and conducted a wide search including ongoing trial registry databases and abstracts from major conferences. We did not apply any language restrictions, and we are confident we have included all relevant trials to date in this review. At least two review authors (AB, CM, DM, RM, RManser) reviewed search results. Multiple authors (AB, RM, DM) checked all data, both during the extraction process and analysis of data against published results. We resolved any disagreements and queries via discussion. One review author (DM) contacted trial authors when additional data were required.

Agreements and disagreements with other studies or reviews

The previous Cochrane Review on lung cancer screening (Manser 2013), evaluated multiple modalities of screening, including sputum cytology, CXR, and CT. Based on their conclusions, there was no evidence to support screening with sputum cytology or CXR, however more data were required for CT screening. As such, this review focused on lung cancer screening with LDCT and incorporated data from more RCTs (Aberle 2011; Becker 2020; Blanchon 2007; De Koning 2020; Field 2021; Gohagan 2005; Infante 2015; LaRocca 2002; Paci 2017; Pastorino 2012; Wille 2016), most of which were still ongoing in the previous review.

When comparing our review to other systematic reviews published (Hoffman 2020; Huang 2019; Jonas 2021; Rota 2019; Sadate 2020; Mazzone 2021), our review incorporated more secondary outcomes and provided analysis at more defined time points and with additional subgroups. Two of the reviews (Hoffman 2020; Huang 2019), included the AME trial (Yang 2018), which does not have complete mortality data at 5 years. Despite some differences in included trials and time points, the reviews still favoured screening to reduce lung cancer-related mortality and did not show differences in mortality after invasive procedures between groups when reported. However, most concluded that there was probably no difference with all-cause mortality, as their 95% CI just reached or crossed 1. Our review included data from the UKLS trial (Field 2021), and had a 95% CI upper limit of 0.99. One review (Hoffman 2020), also evaluated for diagnosis of stage 1 lung cancer, and found it to be more prevalent in the LDCT screening group.

One other review has focused on overdiagnosis in lung cancer screening RCTs (Brodersen 2020). This review included data from five RCTs (Becker 2020; De Koning 2020; Paci 2017; Pastorino 2012; Wille 2016), and estimated that 38% of screen-detected lung cancers may be overdiagnosed in these trials (95% CI 14% to 63%). Brodersen 2020 performed a sensitivity analysis of their rated high-quality trials (Becker 2020; Wille 2016), which had an estimated overdiagnosis rate of 49% (95% CI 11% to 89%). Of note, a recent publication by Gao 2022 investigated possible overdiagnosis of lung cancer by LDCT screening in a population of mostly non-smoking Taiwanese women. They estimated that from 2004 to 2018, between 12% and 21% of women have been overdiagnosed with lung cancer. Women and non-smokers were underrepresented in the trials included in our review.

Our findings were consistent with other reviews on psychosocial outcomes related to lung cancer screening (Quaife 2021; Slatore 2014; Wu 2016).

In regard to assessment of risk of bias, our review was generally consistent with other reviews, however we tended to be more conservative when evaluating 'other biases' in trials, such as protocol deviations and unbalanced baselines. We also contacted authors for clarification.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence in this review from RCTs suggests that screening with LDCT leads to a reduction in lung cancer-related mortality in high-risk populations, although it should be noted that the certainty of this evidence is moderate. There is also an increase in investigations associated with LDCT screening, including those unrelated to lung cancer disease. More information is required to define the ideal frequency and duration of screening, as there is a probable loss of impact of screening on lung cancer-related mortality as time from last screening scan increases.

Whilst available data suggests there is probably no difference between LDCT screening and non-LDCT screening groups in mortality following invasive procedures, there remains a lack of data regarding harms of screening. Quality assurance with monitoring of harms, such as complications, false positives, recall rates and follow-up should be included as part of a screening programme with set key performance indicators.

When discussing lung cancer screening with patients, physicians can consider the relative risks and benefits for the individual prior to recommendation, and ensure that screening and subsequent follow-up occurs in centres with experience in lung nodule and lung cancer care, particularly given concerns regarding overdiagnosis. The difference in management of solid versus subsolid nodules (Silva 2018), and incorporation of recommendations such as the European Union Position Statement on lung cancer screening (Oudkerk 2017), can be considered. Whilst there was limited use of risk prediction models in the included RCTs, these have been associated with improved participant selection (Field 2019; ten Haaf 2017), and further trials are required to evaluate and compare different models. Physicians may choose to also be mindful of potential psychosocial consequences of screening, although evidence has not demonstrated any long-term impacts. Participants of screening programmes should receive counselling about the implications of a positive screen and significant incidental findings (SIFs).

Current smokers and former smokers with a significant pack-year history formed the majority of the population in this review, with trials evaluating lung cancer screening with LDCT in predominantly non-smokers still ongoing. Smoking cessation and other primary prevention strategies can be considered as part of a screening programme, although the optimal method for delivery of these strategies is still under investigation.

There have been several guidelines from the USA and Europe with favourable positions on national screening programmes for groups at high risk of lung cancer (Jonas 2021; Kauczor 2020; Mazzone 2021). Response to recruitment to screening programmes in the trial setting ranged from 1% to 5% of people approached with invitations and letters. Adherence to screening was noted to decrease over time, with only 54% of the annual screening group of the MILD trial completing their 6-year scan (Pastorino 2012). Further consideration is required to determine the optimal way to engage with people at high risk of lung cancer, to ensure equitable access to screening when developing national screening programmes, as well as ensuring engagement with the programme once initiated.

Implications for research

Further research is needed to determine participant selection for a lung cancer screening programme, particularly focusing on groups under-represented in this review, women and non-smokers, as well as other geographic regions outside the USA and Europe.

Additional research is also required for the optimal duration and frequency of screening (van der Aalst 2021), with particular attention to the optimal assessment and management of lung nodules; there is no uniform approach or guideline to nodule management. Further review of nodule classifications, such as Lung CT Screening Reporting and Data System (Lung-RADS, Lung-RADS 2019) and the Brock model (McWilliams 2013) for estimating lung cancer risk from nodules are needed, with particular attention to ground glass opacities and nodule management, which may contribute to overdiagnosis. None of the included trials prospectively evaluated the use of artificial intelligence in lung cancer screening.

Biomarkers are an evolving field, with most included trials only publishing very early descriptive data. Future research with biomarkers may help with the selection of participants for screening or prove useful as a screening modality.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aberle 2011

Study characteristics	
Methods	**Trial design**: phase 3 RCT

Aberle 2011 *(Continued)*

Duration of follow-up: median 12 years

Number of study locations: 33

Participants	**Baseline characteristics** **Number of participants**: LDCT arm (26,723), CXR arm (26,733) **Age** (no. participants) • LDCT arm: < 55 years old (2), 55-59 years old (11,440), 60-64 years old (8170), 65-69 years old (4756), 70-74 years old (2352), > 74 years old (1), missing (2) • CXR arm: < 55 years old (3), 55-59 years old (11,421), 60-64 years old (8198), 65-69 years old (4762), 70-74 years old (2345), > 74 years old (3), missing (1) **Sex**: LDCT arm (male 15,770, female 10,953); CXR arm (male 15,763, female 10,970) **Smoking status**: LDCT arm (current 12,869, former 13,854); CXR arm (current 12,910, former 13,823) **Performance status**: not published **Ethnicity/race**: LDCT arm (white 24,289, black 1196, Asian 559, other 516, missing 163); CXR arm (white 24,260, black 1182, Asian 536, other 546, missing 209) **Environmental exposures** (no. participants) • LDCT arm: asbestos (1238), baking (603), butchering/meat packing (572), chemicals or plastics manufacturing (1642), coal mining (169), cotton or jute processing (194), farming (2837), firefighting (477), flour/feed/grain milling (290), foundry or steel milling (1159), hard rock mining (205), painting (1382), sandblasting (456), welding (1505), any of the above occupations (7448) • CXR arm: asbestos (1288), baking (551), butchering/meat packing (593), chemicals or plastics manufacturing (1675), coal mining (162), cotton or jute processing (201), farming (2862), firefighting (513), flour/feed/grain milling (297), found ary or steel milling (1089), hard rock mining (213), painting (1431), sandblasting (457), welding (1470), any of the above occupations (7557) **Inclusion criteria** • Age 55-74 years • ≥ 30 pack years of cigarette smoking history • Current or former smokers (quit smoking within the previous 15 years) • Ability to lie on the back with arms raised over the head • Signed informed consent form **Exclusion criteria** • Metallic implants or devices in the chest or back, such as pacemakers or Harrington fixation rods • Treatment for, or evidence of, any cancer other than non-melanoma skin cancer or carcinoma in situ (with the exception of transitional cell carcinoma in situ or bladder carcinoma in situ) in the 5 years prior to eligibility assessment • History of lung cancer • History of removal of any portion of the lung, excluding needle biopsy • Requirement for home oxygen supplementation • Participation in another cancer screening trial • Participation in a cancer prevention trial, other than a smoking cessation trial • Unexplained weight loss of more than 15 lb in the 12 months prior to eligibility assessment • Recent haemoptysis • Pneumonia or acute respiratory infection treated with antibiotics in the 12 weeks prior to eligibility assessment • Chest CT examination in the 18 months prior to eligibility assessment

Aberle 2011 *(Continued)*

	Preintervention investigations: nil
Interventions	**Intervention characteristics** Frequency of scanning: annual LDCT setting: 120 kVp to 140 kVp and 20 mAs to 60 mAs Duration of screening: 3 years *Interpretation of scans* • Volumetric or size criteria: size • Use of volumetry software: no • Criteria for significance: findings suspicious of lung cancer, such as non-calcified nodule ≥ 4 mm, lung consolidation, or obstructive atelectasis, nodule enlargement, and nodules with suspicious changes in attenuation • Prespecified protocol for nodule follow-up: no trial-wide algorithm, however there were options provided to LDCT readers **Comparison** • Description: no screening
Outcomes	**Primary outcome** • Lung cancer mortality **Secondary outcomes** • All-cause mortality • Lung cancer incidence • Complications of diagnostic evaluation • Lung cancer stage of distribution • Baseline T0 screening results • T1 screening results • T2 screening results
Identification	**Sponsorship source**: National Cancer Institute, Cancer Imaging Program, University of Colorado Denver, Georgetown University, Pacific Heath Research and Education Institute, Henry Ford Health System, University of Minnesota, Washington University, University of Pittsburgh, University of Utah, Marshfield Clinic Research Foundation, University of Alabama at Birmingham, Westat, Information Management Services **Country**: USA **Setting**: hospital **Trial start date**: August 2002 **Completion of follow-up**: December 2009 **Trial registration number**: NCT00047385 **Corresponding author's name**: Denise Aberle **Institution**: University of California at Los Angeles **Email**: daberle@mednet.ucla.edu
Notes	**Conflicts of interest**

Aberle 2011 *(Continued)*

Denise Aberle reported grants from American College of Radiology Imaging Network (ACRIN), personal fees and other from LUNGevity Foundation, other from Siemens Medical Solutions USA. Personal fees from 2012: First Annual McLennan Lecture, University of Iowa, US Department of Veteran Affairs, Gordon Gamsu Memorial Lecture, Society of Thoracic Radiology Annual Meeting, University of Texas Southwestern Medical Center Meeting, Vanderbilt-Ingram Cancer Center Retreat on Lung Cancer,ARRS Chest Imaging Symposium, Institute of Medicine, Affordable Care for the 21st Century Workshop, California Technology Assessment Forum Policy Symposium, Stanford University, Department of Radiology Grand Rounds Series, New York University, Head to Toe Imaging Conference, Society of Thoracic Surgeons (STS) 48th Annual Meeting, 13th International Lung Cancer Congress, European Society of Thoracic Imaging 2012 Annual Meeting. Personal fees from 2013: Glendale Memorial Hospital and Health Center's Continuing Medical Education, Colorado Radiological Society Visiting Professor Series, University of Colorado, Denver, Grand Rounds Series, 13th International Lung Cancer Congress, International Association for the Study of Lung Cancer 15th World Conference. Non-financial support from 2012: National Cancer Advisory Board Meeting, ACRIN Semi-Annual Meetings, Eastern Cooperative Oncology Group- American College of Radiology Imaging Network Strategic Retreat, Eastern Cooperative Oncology Group-American College of Radiology Imaging Network Imaging Workshop, AACR-IASLC 2nd Annual Joint Conference. Non-financial support from 2013: Institute of Medicine Affordable Care Workshop, 3rd World Congress on Thoracic Imaging (WCTI), National Cancer Institute Lung SPORE Workshop, ACRIN Semi-Annual Meetings. Personal fees from 2014: AACR-IASLC 3rd Joint Conference. Non-financial support from 2014: European Congress of Radiology, University of California Dose Retreat, ECOG-ACRIN Semi-Annual Meetings. Personal fees and non-financial support from 2014: American Thoracic Society. Non-financial support from 2014: DECAMP Consortium Meeting, National Cancer Institute Lung SPORE Workshop, AACR Lung Cancer Screening Meeting, LUNGevity Science Advisory Board Meeting. Personal fees from 2014: LUNGevity Award Program Review. Personal fees from 2015: LARS Midwinter Conference. Non-financial support from 2015: ECOG-ACRIN Semi Annual Meeting, STR Annual Meeting, Cambridge Chest Meeting, ACRIN Semi-Annual Meetings, LUNGevity Award Program Review, Siemens Annual UCLA Research Meeting, IASLC WCLC Annual Meeting, LUNGevity Scientific Advisory Board Meeting, AACR Annual Meeting, DECAMP Consortium Meeting, NIH SPORE. Other from 2016 Veracyte Advisory Board, American Society of Clinical Oncology (ASCO) Annual Meeting. Grants from 2015: Lung Nodule Surveillance Trail (LNST) Kick off Meeting, MCL Consortium Meeting. From 2015: Veracyte. Non-financial support from 2016: Harvard University Chest Imaging Course, Moffitt Cancer Center, Yale University Grand Rounds, Kaiser Radiology Symposium grants, MCL Consortium Meeting,ECOG-ACRIN Semi Annual Meeting, DECAMP Consortium Meeting, National Academy of Sciences Workshop, Siemens Annual UCLA Research Meeting. Personal fees from 2016: Torrance Medical Center Grand Rounds, Veracyte Advisory Board Meeting. Personal fees and non-financial support from 2016: International Lung Cancer Congress (ILCC) Meeting. Grants and non-financial support from 2016: MCL Consortium Meeting.

Jolean Sicks reported a grant to the institution from NCI, U10CA18-820-0151, during the trial.

Caroline Chiles reported a grant to the institution from NIH, CA 80098, during the trial.

The remaining authors had nothing to disclose.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation using 6 or 8 block groups and stratified by site, sex, and 5 year age groups
Allocation concealment (selection bias)	Low risk	Allocation concealment generated by a central process
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were not blinded
Blinding of outcome assessment (detection bias)	Low risk	Review board was blinded when assessing the cause of death.

Aberle 2011 *(Continued)*

All outcomes		Active follow-up was until December 2009, with subsequent cause of death established from cancer registries
Incomplete outcome data (attrition bias) All outcomes	Low risk	No significant loss to follow-up < 20%. 192 of enrolled persons who where thought to be eligible at the time of randomisation were determined to be ineligible. Reasons included: CT within 18 months (n = 68), non-smokers or quit > 15 years before randomisation (n = 23), participation in another cancer screening trial (n = 28), recent antibiotic use (n = 17), insufficient pack years (n = 12), diagnosis of cancer in the 5 years before randomisation (n = 14), age older or younger than the required range (n = 12). These randomised but ineligible participants were included in the trial and analysis.
Selective reporting (reporting bias)	Low risk	All outcomes reported, however only selected sites measured quality of life
Other bias	Low risk	Minimal protocol deviations

Becker 2020

Study characteristics	
Methods	**Trial design:** phase 3 RCT **Duration of follow-up:** median follow-up 9 years **Number of trial locations**: 1
Participants	**Baseline characteristics** **Number of participants**: LDCT (2029); control (2023) **Age** (no. participants) • LDCT: 50-54 years old (942), 55-59 years old (518), 60-64 years old (344), 65-69 years old (225) • Control: 50-54 years old (932), 55-59 years old (528), 60-64 years old (341), 65-69 years old (222) **Sex**: LDCT (1315 males, 714 females); control (1307 males, 716 females) **Smoking status**: LDCT (1259 current smokers, 770 former smokers); control (1248 current smokers, 775 former smokers)) **Performance status**: not reported **Ethnicity/race**: not reported **Environmental exposures**: not reported **Inclusion criteria** • Age 50-69 years old • Smoking history of at least 40 pack years • If under the age of 60, current smokers or ceased smoking within the last 5 years • Able to complete a self-administered epidemiology questionnaire providing details on smoking history, family history of lung and other cancers (if any), occupational history and previous illnesses • Agree to be randomised to screening with annual low-dose spiral CT plus smoking cessation counselling or only smoking cessation counselling • Have signed an informed consent form

Becker 2020 *(Continued)*

	Exclusion criteria • History of lung cancer or other malignancy (except basal cell carcinoma) • History of a disease that would preclude surgical as well as medical treatment of lung cancer • Other serious illness that would reduce life expectancy to < 10 years **Preintervention investigations**: nil
Interventions	**Intervention characteristics** • Frequency of scanning: annual • LDCT setting: not provided. 1.6 mSV to 2 mSV radiation exposure reported per scan • Duration of screening: 5 years *Interpretation of scans* • Volumetric or size criteria: size and volumetric criteria • Use of volumetry software: yes • Criteria for significance: any nodule ≥ 5 mm • Prespecified protocol for nodule follow-up: yes **Comparison** • Description: no screening
Outcomes	**Primary outcomes** • Mortality from lung cancer at 5 and 10 years **Secondary outcomes** • Nil
Identification	**Sponsorship source**: German Research Foundation, Dietmar Hopp Foundation **Country**: Germany **Setting**: hospital **Trial start date**: Sept 2007 **Completion of follow-up**: April 2018 **Trial registration number**: ISRCTN30604390 **Corresponding author's name**: Rudolf Kaaks **Institution**: German Cancer Research Center, Heidelberg, Germany **Email**: r.kaaks@dkfz-heidelberg.de
Notes	**Conflicts of interest** Claus-Peter Heussel reported research funding, outside the present trial, from Siemens, Pfizer, MeVis Medical Solutions, Boehringer Ingelheim, lecture fees from Gilead Sciences, Essex Pharma, Schering-Plough, AstraZeneca, Eli Lilly and Company, Roche, Merck Sharp & Dohme, Pfizer, Bracco, MEDA Pharma, InterMune, Chiesi Farmaceutici, Siemens, Covidien, Pierre Fabre, Boehringer Ingelheim, Grifols, Novartis, Basilea, and Bayer and consultation or other fees from Schering-Plough, Pfizer, Basilea, Boehringer Ingelheim, Novartis, Roche, Astellas, Gilead, Merck Sharp & Dohme, Eli Lilly and Company, Intermune, and Fresenius and ownership of stocks from GSK. The other authors declared no potential conflicts of interest.

Becker 2020 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation using block randomisation stratified by age < 60 versus ≥ 60 years and smoking status former versus current
Allocation concealment (selection bias)	Low risk	Electronic randomisation using the RANDI tool
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The lung cancer death review committee was blinded to allocation arm. However, there is a risk of bias and potential for underestimation of lung cancer as the cause of death. Cases were only reviewed by the committee if lung cancer was mentioned in the case. Furthermore, method of detection of lung cancer was not uniform, with only 1 out of 85 cases of lung cancer identified by death certificate in the intervention arm and 11 of the 67 cases in the control arm.
Incomplete outcome data (attrition bias) All outcomes	Low risk	13 participants lost to follow-up for mortality data (5 in intervention arm, 8 in control arm) and data linkage to registries were not available in 39 participants as they declined data access.
Selective reporting (reporting bias)	Low risk	The trial reported on one prespecified outcome
Other bias	Low risk	No protocol deviations

Blanchon 2007

Study characteristics

Methods	**Trial design:** feasibility RCT **Duration of follow-up:** not published **Number of trial locations**: 14
Participants	**Baseline characteristics** **Number of participants**: LDCT arm (385); CXR arm (380) **Age**: median age LDCT arm (56 years old); CXR arm (56 years old) **Sex**: LDCT arm (274 males, 111 females); CXR arm (267 males, 113 females) **Smoking status**: LDCT arm (238 current, 129 former); CXR arm (224 current, 127 former) **Performance status**: not published **Ethnicity/race**: not published **Environmental exposures**: not published **Inclusion criteria**

Blanchon 2007 *(Continued)*

- Age 50-75 years old
- Asymptomatic current or former smokers (having quit < 15 years from enrolment) and cigarette consumption ≥ 15 cigarettes/day for at least 20 years

Exclusion criteria

- Past history of malignancy
- Respiratory, cardiovascular or general impairment that might compromise thoracic surgery or a thoracic diagnostic procedure
- Previous history of congestive heart failure or recent myocardial infarction
- Active pulmonary infection
- Previous history of heavy asbestos exposure
- Previous history of chest disease that might mimic radiological appearance of lung cancer

Preintervention investigations

- Nil

Interventions

Intervention characteristics

- Frequency of scanning: annual
- LDCT setting: 100 kV to 140 kV, 20 mA to 100 mA
- Duration of screening: 3 years

Interpretation of scans

- Volumetric or size criteria: size
- Use of volumetry software: no
- Criteria for significance: non-calcified nodule > 5 mm
- Prespecified protocol for nodule follow-up: yes

Comparison

- Description: annual CXR for 3 years

Outcomes

Primary outcomes

- Feasibility of enrolment by general practitioners and compliance of screened subjects
- Contamination rates between LDCT and CXR arms
- Feasibility of follow-up and diagnostic strategies of radiological abnormalities by accredited multidisciplinary hospital teams with the number of lung cancers diagnosed and rate of early lung cancers
- Number of futile thoracotomies for benign lesions
- Number of adverse events and rates of severe adverse events during diagnostic procedures

Secondary outcomes

- Nil

Identification

Sponsorship source: Programme Hospitalier de Recherche Clinique and Pneumonologie Developpement

Country: France

Setting: hospital

Trial start date: October 2002

Completion of follow-up: not published

Trial registration number: 2526

Blanchon 2007 *(Continued)*

	Corresponding author's name: Thierry Blanchon **Institution**: Universite Pierre and Marie Curie, Paris, France **Email**: blanchon@u707.jussieu.fr
Notes	**Conflicts of interest**: Nil declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method was not stated.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if assessors of harm outcomes were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Only baseline data published. 144 participants withdrew consent post-randomisation; authors were contacted
Selective reporting (reporting bias)	Unclear risk	Only baseline data published; authors were contacted
Other bias	Unclear risk	Only baseline data published; authors were contacted

De Koning 2020

Study characteristics

Methods	**Trial design**: phase 3 RCT **Duration of follow-up**: 10 years **Number of trial locations**: 4
Participants	**Baseline characteristics** **Number of participants**: LDCT arm (7900); control arm (7892) **Age**: median age LDCT arm (58 years old); control arm (58 years old) **Sex**: LDCT arm (6583 males, 1317 females); control arm (6612 males, 1277 females, 3 missing) **Smoking status**: LDCT arm (4415 current, 3465 former, 20 missing); control arm (4333 current, 3536 former, 23 missing)

De Koning 2020 *(Continued)*

Performance status: Dutch control arm only N = 7393 (1124 had excellent/very good health, 4922 had good health, 1347 had moderate/poor health). Dutch control arm only N = 7398 (3292 had high physical activity levels, 3318 had moderate physical activity levels, 788 had low physical activity levels)

Ethnicity/race: not published

Environmental exposures: not published

Inclusion criteria

- Born between 1928 and 1956
- Smoked > 15 cigarettes/day during > 25 years or smoked > 10 cigarettes/day over > 30 years
- Current or former smokers who quit smoking ≤ 10 years ago

Exclusion criteria

- Moderate or bad self-reported health who were unable to climb two flights of stairs
- Body weight ≥ 140 kg
- Current or past renal cancer, melanoma or breast cancer
- Lung cancer diagnosed < 5 years ago or ≥ 5 years ago but still under treatment
- Had a chest CT examination < 1 year before they filled in the first NELSON questionnaire

Preintervention investigations

- Nil

Interventions	**Intervention characteristics** • Frequency of scanning: baseline, year 1, year 3 and year 5.5 • LDCT setting: 30 mA and 120 kVP to 140 kVP • Duration of screening: 5.5 years *Interpretation of scans* • Volumetric or size Criteria: volumetric • Use of volumetry software: yes • Criteria for significance: any non-calcified nodule with no benign characteristics • Prespecified protocol for nodule follow-up: yes **Comparison** • Description: no screening
Outcomes	**Primary outcome** • Lung cancer mortality **Secondary outcomes** • Lung cancer incidence (stage-specific; time interval; screen-detected versus interval cancers) and survival • Detection rates for first (prevalence) and subsequent (Incidence) screening, as well as stage distribution • Sensitivity, specificity and positive predictive value • Quality of Life • Quality-adjusted life years • Cost-effectiveness
Identification	**Sponsorship source**: Stichting Centraal Fonds Reserves van Voormalig Vrijwillige Ziekenfondsverzekeringen (RvvZ), Siemens Germany, G. Ph. Verhagen Stichting, Rotterdam Oncologic Thoracic Steering committee (ROTS), Erasmus Trust fund, Stichting tegen Kanker, Vlaamse Liga tegen Kanker

De Koning 2020 *(Continued)*

Country: The Netherlands and Belgium

Setting: hospital

Trial start date: August 2003

Completion of follow-up: December 2015

Trial registration number: ISRCTN63545820

Corresponding author's name: Harry J Koning

Institution: Erasmus Medical Center, University Medical Center Rotterdam, Rotterdam, The Netherlands

Email: h.dekoning@erasmusmc.nl

Notes

Conflicts of interest

Carlijn van der Aalst reported receiving supplies from Siemens.

Pom A. de Jong reported receiving grant support, paid to his institution, from Philips.

Mathias Prokop reported receiving fees for serving on a speakers bureau from Bayer HealthCare and Bracco Imaging and grant support and fees for serving on a speakers bureau from Canon Medical Systems and Siemens.

Joachim G.J.V. Aerts reported receiving consulting fees from Amphera, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, F. Hoffmann–La Roche, Merck, and Takeda Oncology, holding pending patent #PCT/NL20/19/050636 on specific inhibition of Janus kinase 3 for modulating antitumour immune responses, and holding patent #9962433 on a method for preparing an immunogenic lysate, the lysate obtained, dendritic cells loaded with such lysate, and a pharmaceutical composition comprising the lysate or the dendritic cells.

Rozemarijn Vliegenthart reported receiving fees for serving on a review committee from BTG International and grant support, paid to her institution, from Siemens.

Kevin ten Haaf reported receiving supplies from Siemens.

Matthijs Oudkerk reported receiving lecture fees from AstraZeneca and Siemens Medical Solutions USA.

No other potential conflict of interest were reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Documented 1:1 randomisation
Allocation concealment (selection bias)	Low risk	Central allocation concealment method used, information from author
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	There were some concerns about the method of determining lung cancer-related mortality. The 2012 publication by Horeweg et al. in *Lung Cancer* reviewed the preliminary 50 completed medical files of Dutch participants who

De Koning 2020 *(Continued)*

		were deceased and had a diagnosis of lung cancer. This trial reported a reduced specificity for death certificates (62.5%) and sensitivity of 95.2% compared with a clinical expert committee. This was subsequently followed by a larger sample of 263 participant deaths and the specificity rose to 98.8% and sensitivity of 92.6%. The committee reclassified 12.2% of causes of death. However, the remaining 163 male deaths then had cause of death determined by death certificate only. The assessors were unblinded in subsequent publication. There were no significant concerns about assessment of other outcomes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	18 persons could not be linked because a digital form could not be retrieved for national linkages, > 98% coverage
Selective reporting (reporting bias)	Low risk	Cost analysis will be published, information from author
Other bias	High risk	There was an inadequate balance of males and females included in this trial. Additionally, method of assessment of primary lung cancer-related mortality outcome was changed during the trial. The initial trial protocol planned only 4 years of screening, however an additional scan was introduced and screening extended to 6.5 years. Information provided by author clarified that the fourth round of screening was sought in 2009, after the trial had commenced. This change to screening is unlikely to have increased risk of bias.

Field 2021

Study characteristics	
Methods	**Trial design**: pilot RCT **Duration of follow-up**: median 7 years **Number of trial locations:** 2
Participants	**Baseline characteristics** **Number of participants**: LDCT arm (2028); control arm (2027) **Age**: median age • LDCT arm (median age 67 years old): 50-59 years old (44), 60-69 years old (1295), 70-76 years old (689) • Control arm (median age 67 years old): 50-59 years old (58), 60-69 years old (1291), 70-76 years old (678) **Sex**: LDCT arm (1529 males, 499 females); control arm (1507 males, 520 females) **Smoking status**: LDCT arm (2 never-smokers, 777 current, 1249 former); control arm (0 never-smokers, 791 current, 1236 former) **Performance status**: not published **Ethnicity/race**: LDCT arm (1992 white, 18 non-white, 18 missing data); control arm (1992 white, 19 non-white, 16 missing data) **Environmental exposures**: LDCT arm: asbestos (763); control arm: asbestos (763) **Inclusion criteria**

Field 2021 *(Continued)*

- Risk criteria based on the Liverpool Lung Project (LLP) Risk Prediction Model (includes age, sex, smoking duration, history of previous pneumonia, history of previous cancer, family history, exposure to asbestos)
- Males and females aged between 50 and 75 years old
- Fully informed written consent given

Exclusion criteria

- Unable to give consent
- Comorbidity which would unequivocally contraindicate either screening or treatment if lung cancer were detected
- A CT scan of the chest performed within 1 year of the invitation to be screened
- Any condition precluding written informed consent
- Inability to lie flat
- Weight > 200 kg

Preintervention investigations

- Nil

Interventions	**Intervention characteristics** • Frequency of scanning: annual • LDCT setting: 90 kVp to 140 kVp, mA setting adjusted to achieve volume CT dose index • Duration of screening: 1 year *Interpretation of scans* • Volumetric or size criteria: both • Use of volumetry software: yes • Criteria for significance: solid intraparenchymal nodules ≥ 15 mm^3 or pleural or juxtapleural nodules with a maximal diameter of ≥ 3.1 mm. Part solid nodules. • Prespecified protocol for nodule follow-up: yes **Comparison** • Description: no screening
Outcomes	**Primary outcomes** • To establish the impact of preclinical detection of lung cancer mortality by comparing lung cancer mortality between the control group and the screened groups combined • To establish if there is a lung cancer mortality benefit from CT screening • Establish total mortality benefit • Cost-effectiveness of a national lung cancer screening programme **Secondary outcomes** • To determine the physical morbidity associated with lung cancer screening • To determine the resource implications of screening and the resulting intervention • To assess the feasibility of population screening for lung cancer as reflected by uptake of invitations and compliance rates with annual screening • Establish a blood and tissue bank for the future assessment of early detection diagnostics and novel tumour biomarkers
Identification	**Sponsorship source**: NIHR Health Technology Assessment programme, NIHR policy research program, Roy Castle Lung cancer foundation, Royal Liverpool & Broadgreen University Hospital Trust (UK) **Country**: England

Field 2021 *(Continued)*

Setting: hospital

Trial start date: October 2011

Completion of follow-up: February 2020

Trial registration number: ISRCTN78513845

Corresponding author's name: John Field

Institution: The University of Liverpool Cancer Research Centre, Liverpool, UK

Email: j.k.field@liv.ac.uk

Notes

Conflicts of interest

John K Field reported receiving fees from AstraZeneca (Speaker's Bureau) and advisory boards of Epigenomics; NUCLEIX Ltd. AstraZeneca, iDNA; Grant Support: Janssen Research & Development, LLC.

Robert C Rintoul reported being on the advisory boards of AstraZeneca and Roche.

David R Baldwin reported receiving speaker remuneration from AstraZeneca, Roche, MSD, BMS, Johnson and Johnson.

Kate E Brain reported receiving personal fees from Astra Zeneca outside this work.

Tim Eisen reported receiving research support from AstraZeneca, Bayer, Pfizer; being employed by Roche (from March 2020) and was employed by AstraZeneca (to March 2020) and having stock in AstraZeneca and Roche; was a trustee of Macmillan Cancer Support.

Arjun Nair reported having current grants and contracts with BRC, DART; Honoraria Aidence BV, AstraZeneca; Support from BLF, and as the clinical lead for NTLHC.

No competing interests were reported from other co-authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation using a computer-generated random number algorithm
Allocation concealment (selection bias)	Low risk	Allocation concealment via UKLS database management system
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary outcome lung cancer mortality. Acknowledging the limitations of determining lung cancer mortality from death registry data without blinded committee review. All-cause mortality and lung cancer incidence were determined without knowledge of trial allocation, since these came from routine cancer registration and death certification.

Field 2021 *(Continued)*

		Interpretation of LDCT was performed by two separate radiologists (one local and one central). The central radiologist had access to the local radiologist's report.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were not significant and participants lost to follow-up had contact attempted by site primary investigator and if unsuccessful, the trial team contacted the participant's general practitioner for follow-up information. It should be noted however, that 87 patients were excluded due to no consent for data linkage or having censoring events after consent. Authors were contacted, and censoring events were clarified as data were unavailable via national databases.
Selective reporting (reporting bias)	Low risk	All reported
Other bias	High risk	Minor amendments including changing nodule protocol to include new nodules detected on subsequent scans and clarification of exclusion criteria as recent CT chest. Authors reported a computer error which used LLP risk model version 2 instead of version 1. Trial reported to use intention-to-treat analysis, although the 87 participants were not included in long-term mortality and cancer incidence analysis.

Gohagan 2005

Study characteristics	
Methods	**Trial design**: feasibility RCT **Duration of follow-up**: 1 year active, median 5 years with database linkage **Number of trial locations**: 6
Participants	**Baseline characteristics** **Number of participants**: LDCT arm (1660); CXR arm (1658) **Age** • LDCT arm: 55-59 years old (616), 60-64 years old (514), 65-69 years old (337), 70-74 years old (193) • CXR arm: 55-59 years old (624), 60-64 years old (500), 65-69 years old (348), 70-74 years old (186) **Sex**: LDCT arm (965 males, 695 females); CXR arm (978 males, 680 females) **Smoking status**: LDCT arm (961 current, 699 former); CXR arm (947 current, 711 former) **Performance status**: not published **Ethnicity/race**: not published **Environmental exposures**: not published **Inclusion criteria** • Age 55-74 years old at time of randomisation • Current or former smoker who had quit within previous 10 years • ≥ 30 pack-year smoking history

Gohagan 2005 *(Continued)*

	Exclusion criteria • History of CT chest in the previous 24 months • History of lung cancer • Currently receiving treatment or any cancer other than non-melanoma skin cancer • Removal of a portion of a lung or entire lung • Participation in another cancer screening trial (including PLCO cancer trial) or a primary cancer prevention trial other than a smoking cessation trial **Preintervention investigations** • Nil
Interventions	**Intervention characteristics** • Frequency of scanning: annual • LDCT setting: 120 kVp to 140 kVp, 60 mA • Duration of screening: 2 years *Interpretation of scans* • Volumetric or size criteria: size • Use of volumetry software: no • Criteria for significance: any non-calcified nodule ≥ 4 mm or other abnormalities suspicious for lung cancer at the discretion of the radiologist • Prespecified protocol for nodule follow-up: no **Comparison** • Description: annual CXR
Outcomes	**Primary outcomes** • Feasibility of rapidly accruing high-risk participants who were not actively being screened with spiral CT scans into a trial of lung cancer screening • Willingness of participants to be randomised to either a LDCT or CXR and undergoing appropriate examination • Likelihood that participants randomised to CXR would subsequently receive a spiral CT scan on their own (and vice versa) • Prevalence of abnormal findings on baseline screening • Extent of diagnostic follow-up after abnormal screening findings **Secondary outcomes** • Nil
Identification	**Sponsorship source**: National Cancer Institute **Country**: USA **Setting**: University hospitals **Trial start date**: August 2000 **Completion of follow-up**: December 2002 **Trial registration number**: NCT00006382 **Corresponding author's name**: Paul Pinksy **Institution**: National Cancer Institute, Bethesda, USA

Gohagan 2005 *(Continued)*

	Email: pp4f@nih.gov
Notes	**Conflicts of interest** Jennifer M Croswell reported financial relationships involving spouse (husband owns shares in Johnson & Johnson) Barnett S Kramer reported receiving money from the Journal of the National Cancer Institute. Nil other disclosures reported for other authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation stratified for age (in 5-year categories), sex and screening centre using blocks of varying sizes. Once eligibility was established and consent was obtained by a trial centre, participants were randomly assigned to a treatment group through a single, centralized, secure, web-based system (which generated random code) operated by the trial co-ordinating centre. This process ensured allocation concealment for trial site investigators. Randomisation was stratified by age group (in 5-year categories), sex, and trial centre by using variable block sizes.
Allocation concealment (selection bias)	Low risk	Once eligibility was established and consent was obtained by a trial centre, participants were randomly assigned to a treatment group through a single, centralised, secure, web-based system (which generated random code) operated by the trial co-ordinating centre. This process ensured allocation concealment for trial site investigators. Randomisation was stratified by age group (in 5-year categories), sex, and trial centre by using variable block sizes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Assessors were not blinded to any of the outcomes. Lung cancer-related deaths were determined by death certificate during the trial, with a registry linkage performed in 2007 for long-term follow-up data.
Incomplete outcome data (attrition bias) All outcomes	Low risk	91 of initial 3409 participants initially randomised to LSS (46 participants in intervention, 45 participants in control), were subsequently found to be ineligible due to participation in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO, Oken 2011). Analysis excluded this cohort.
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	There was a change in definition of positive scan between T0 and T1 scans, however this was unlikely to have impacted outcomes.

Infante 2015

Study characteristics

Methods	**Trial design:** phase 3 RCT

Infante 2015 *(Continued)*

Duration of follow-up: median 8.5 years

Number of trial locations: 3

Participants	**Baseline characteristics** **Number of participants**: LDCT arm (N = 1264); control arm (N = 1186) **Age**: mean age for both groups 65 years old **Sex**: 100% male **Smoking status**: LDCT arm (714 active smokers); control (681 active smokers) **Performance status**: not reported **Ethnicity/race**: not reported **Environmental exposures**: LDCT arm (391 participants had occupational exposures including chemical industry, insulation, construction, metallurgy, agriculture, mining); control arm (402 participants had occupational exposures including chemical industry, insulation, construction, metallurgy, agriculture, mining) **Inclusion criteria** • Age 60-74 years old • Smokers ≥ 20 pack years (current or quit < 10 years prior to accrual • Male **Exclusion criteria** • Severe comorbidity, life expectancy < 5 years • Severe heart failure • Chronic respiratory insufficiency • Oxygen saturation levels < 94% at rest • Renal dialysis • Uncontrolled hypertension • Severe vascular disease in active smoker • Uncompensated diabetes • Other severe metabolic disturbances • Inability to comply with the follow-up protocol • Dementia • Drug or alcohol addiction • Schizophrenia or other severe psychiatric conditions • Conditions carrying severe disability • Previous malignancy (except non-melanoma skin cancer) - any organ site, if treated < 10 years prior to accrual, early squamous cancer of the larynx/oral cavity < 5 years **Preintervention investigations** • Baseline CXR and sputum cytology with clinical examination in both arms
Interventions	**Intervention characteristics** • Frequency of scanning: annual • LDCT setting: 140 kvp, 40 mA • Duration of screening: 5 years *Interpretation of scans* • Volumetric or size criteria: size criteria

Infante 2015 *(Continued)*

- Use of volumetry software: no
- Criteria for significance: abnormalities suggestive of malignancy, such as non-calcified pulmonary nodules ≥ 10 mm in diameter or smaller but showing spiculated margins, or non-nodular lesions such as a hilar mass, focal ground glass opacities, major atelectasis, endobronchial lesions, mediastinal adenopathy, pleural effusion or pleural masses
- Prespecified protocol for nodule follow-up: yes

Comparison

- Description: no screening other than yearly clinical examination

Outcomes	**Primary outcomes** • Lung cancer morality • All-cause mortality **Secondary outcomes** • Lung cancer incidence • Stage at detection • Resectability rates
Identification	**Sponsorship source**: Italian Association for the fight against cancer **Country**: Italy **Setting**: hospital **Trial start date**: March 2001 **Completion of follow-up**: May 2013 **Trial registration number**: NCT00420862 **Corresponding author's name**: Maurizio Infante **Institution**: Instituto Clinico Humanitas, Rozzano, Milano, Italy **Email**: maurizio.infante@cancercenter.humanitas.it
Notes	**Conflicts of interest**: nil declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation of four
Allocation concealment (selection bias)	Low risk	Allocation stratified by centre according to computer-generated lists supplied by the data centre
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Assessors were not blinded to cause of death nor to subjects' allocation. Cause of death was determined by death certificates which were cross-checked with available medical records. A death review panel blinded to allocation arm was only consulted when there were several competing causes

Infante 2015 *(Continued)*

		of death. Only 78% of death certificates were cross-checked, 91% of lung cancer-related deaths and 80% of non-pulmonary cancer-related deaths and 76% of non-cancer-related deaths. Active follow-up was terminated in February 2012, with information regarding death being obtained from registries subsequently.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Final report was revised due to discovery of 20 duplicate registrations and 2 test records (2015 AJRCC). Compliance data- 1223 (97%) of participants had ≥ 3 CTs, 1184 (94%) had 5 CT scans. Used intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported.
Other bias	High risk	Inappropriate inclusion of 10 participants (kept in trial) with a history of malignancy treated < 10 years before accrual (4 with superficial bladder cancer, 2 with prostate cancer, 1 with chronic lymphocytic leukaemia, 1 with aggressive fibromatosis, 1 with renal cancer and 1 with head and neck cancer). All male participants. Unbalanced baseline between arms with more respiratory comorbidities 35.28% (intervention) versus 31.20% (control) P = 0.032.

LaRocca 2002

Study characteristics	
Methods	**Trial design:** phase 3 RCT **Duration of follow-up**: not published **Number of trial locations**: not published

Participants	**Baseline characteristics**
	
	Number of participants: 871 participants (allocation arm not specified)
	
	Age: not published
	
	Sex: not published
	
	Smoking status: not published
	
	Performance status: not published
	
	Ethnicity/race: not published
	
	Environmental exposures: not published
	
	Inclusion criteria
	
	• 40 to 70 years old
	• Men and women
	• Patients at high risk for the development of lung cancer as defined by the following.
	  ○ ≥ 30 pack years smoking (may have stopped smoking within past 10 years) at time of trial entry
	  ○ FER < 70% predicted or FEV_1 < 80% predicted obtained from 3 serial performances with < 5% difference
	
	Exclusion criteria
	
	• Abnormal baseline CXR

LaRocca 2002 *(Continued)*

	Preintervention investigations • Baseline CXR (was required to be normal or stable for participant to be randomised)
Interventions	**Intervention characteristics** • Frequency of scanning: annual • LDCT setting: not published • Duration of screening: 5 years *Interpretation of scans* • Volumetric or size criteria: size • Use of volumetry software: no • Criteria for significance: lung nodule diameter ≥ 5 mm and/or features suspicious of malignancy • Prespecified protocol for nodule follow-up: not published **Comparison** • Description: annual CXR
Outcomes	**Primary outcomes** • Determine the efficacy of a lung cancer risk assessment questionnaire combined with spirometry testing in identifying a statistically significant number of persons with high-risk behaviours for the development of lung cancer • Determine the sensitivity of these screening techniques in identifying a population at high risk for the development of lung cancer • Determine the number of patients necessary to screen in order to identify the high-risk population eligible for this trial • Determine the lead time bias of CT scans versus chest x-rays in these patients • Determine the efficacy of spiral CT scanning of the chest in detecting early lung cancers not visible on chest x-rays in patients at high risk for lung cancer • Compare annual spiral CT scanning versus annual chest x-rays in detecting lung cancer in these patients • Compare survival and fatality in these patients with these detection methods • Lung cancer-specific mortality • To determine the public's willingness to participate in a randomised screening trial **Secondary outcomes** • Nil
Identification	**Sponsorship source**: Kentucky Lung Cancer Research Board, Jewish Hospital and St. Mary's Healthcare Kentucky USA **Country**: USA **Setting**: not published **Trial start date**: November 1991 **Completion of follow-up**: not published **Trial registration number**: NCT00006087 **Corresponding author's name**: Renato V. LaRocca **Institution**: Kentuckiana Cancer Institute, Louisville, Kentucky, USA **Email**: not available

LaRocca 2002 *(Continued)*

Notes	**Conflicts of interest**: nil reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method was not stated
Allocation concealment (selection bias)	Unclear risk	Allocation method concealment method was not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information regarding the blinding status of the assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information available
Selective reporting (reporting bias)	Unclear risk	All outcomes either not published or incomplete data
Other bias	Unclear risk	Limited information available; authors were contacted

Paci 2017

Study characteristics

Methods	**Trial design**: phase 3 randomised control trial **Duration of follow-up**: median follow-up 11 years **Number of trial locations**: 3
Participants	**Baseline characteristics** **Number of participants**: LDCT arm (1613); control arm (1593) **Age** • LDCT arm: 55-59 years old (734), 60-65 years old (580), > 65 years old (299) • Control arm: 55-59 years old (670), 60-65 years old (626), > 65 years old (297) **Sex**: LDCT arm (1035 males, 578 females); control arm (1039 males, 554 females) **Smoking status**: LDCT arm (1060 current, 553 former); control arm (1019 current, 575 former) **Performance status**: not published **Ethnicity/race**: not published

Paci 2017 *(Continued)*

	Environmental exposures: not published **Inclusion criteria** • 55 to 69 years old at time of enrolment • Resident in the trial catchment area • Current smoker or former smoker (quit < 10 years) with at least a 20 pack-year history **Exclusion criteria** • Former smokers who quit > 10 years ago or never-smokers • Previous cancer other than non-melanoma skin cancer • General conditions precluding thoracic surgery **Preintervention investigations** • Nil
Interventions	**Intervention characteristics** • Frequency of scanning: annual • LDCT setting: 120 kVP to 140 kVP, 20 mA to 43 mA • Duration of screening: 4 years *Interpretation of scans* • Volumetric or size criteria: size • Use of volumetry software: no • Criteria for significance: at least one non-calcified nodule ≥ 5 mm or a non-solid nodule ≥ 10 mm or the presence of a part-solid nodule • Prespecified protocol for nodule follow-up: yes **Comparison** • Description: no screening
Outcomes	**Primary outcome** • Lung cancer-specific mortality **Secondary outcomes** • All-cause mortality • Lung cancer incidence excess/overdiagnosis
Identification	**Sponsorship source**: Local government of Tuscany, Italian Ministry of Education, University and Research **Country**: Italy **Setting**: screening centres **Trial start date**: September 2003 **Completion of follow-up**: December 2014 **Trial registration number**: NCT02777996 **Corresponding author's name**: Eugenio Paci **Institution**: Prevention and Research Institute, Florence, Italy **Email**: paci.eugenio@gmail.com

Paci 2017 *(Continued)*

Notes	**Conflicts of interest**: nil reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation using software
Allocation concealment (selection bias)	Low risk	Central randomisation using software
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were aware of the allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All participants followed up via cancer registry of the Tuscany region for incidence and mortality. Each CT was read independently by two radiologists on a work station with a consensus reached in case of disagreement. Independent committee reviewed and revised cause of death in a blinded fashion for those cases which met their prespecified criteria following assessment of death certificate and available hospital notes. 31 deaths out of 335 deaths (9%) underwent review with the committee by December 2014. Following cessation of active follow-up in December 2014, deaths were determined via linkages to registries. The same prespecified algorithm was used for determining cause of death, however whether any cases were reviewed by the committee was unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Moderately significant dropouts and low adherence (81% to screening adherence), however intention-to-treat analysis was applied.
Selective reporting (reporting bias)	Low risk	All outcomes published
Other bias	Low risk	No protocol deviations

Pastorino 2012

Study characteristics

Methods	**Trial design**: phase 3 RCT **Duration of follow-up**: 10 years **Number of trial locations**: 1
Participants	**Baseline characteristics** **Number of participants**: biennial LDCT arm (1186); annual LDCT arm (1190); control arm (1723) **Age** • Biennial LDCT arm: < 55 years old (379), 55-59 years old (363), 60-64 years old (261), 65-69 years old (143), ≥ 70 years old (40)

Pastorino 2012 *(Continued)*

- Annual LDCT arm: < 55 years old (394), 55-59 years old (338), 60-64 years old (274), 65-69 years old (134), ≥ 70 years old (50)
- Control arm: < 55 years old (656), 55-59 years old (478), 60-64 years old (359), 65-69 years old (174), ≥ 70 years old (56)

Sex: biennial LDCT arm (813 males, 373 females); annual LDCT arm (814 males, 376 females); control arm (1090 males, 633 females)

Smoking status: biennial LDCT arm (810 current, 376 former); annual LDCT arm (820 current, 370 former); control arm (1546 current, 177 former)

Performance status: not published

Ethnicity/race: not published

Environmental exposures: not published

Inclusion criteria

- Age ≥ 49 years
- Current or former smokers (having quit within 10 years of recruitment) with at least 20 pack years of smoking
- No history of cancer within previous 5 years
- Adequate performance status (assessed on the basis of the patient's eligibility to undergo thoracic surgery)

Exclusion criteria

- History of malignant disease in the previous years
- Not adequate performance status (assessed on the basis of the patient's eligibility to undergo thoracic surgery)

Preintervention investigations

- Nil

Interventions

Intervention characteristics

- Frequency of scanning: biennial and annual arms
- LDCT setting: 120 kV, 30 mAs
- Duration of screening: 10 years (median 4 scans in biennial arm, 7 scans in annual arm)

Interpretation of scans

- Volumetric or size criteria: volumetric
- Use of volumetry software: yes
- Criteria for significance: non-calcified nodules with a volume ≥ 60 mm^3 or findings such as non-calcified hilar or mediastinal lymphadenopathy, atelectasis, consolidation or pleural findings
- Prespecified protocol for nodule follow-up: yes

Comparison

- Description: no screening

Outcomes

Primary outcome

- Lung cancer 10-year mortality

Secondary outcomes

- All-cause mortality
- Lung cancer diagnosis

Pastorino 2012 *(Continued)*

- Smoking cessation - evaluate the impact on smoking cessation of early lung cancer detection through LDCT at annual or biennial intervals versus no screening
- Molecular risk profile through assessing the value of circulating DNA in blood samples
- Molecular risk profile through assessing the value of microRNA in blood and tissue samples

Identification	**Sponsorship source**: Italian Ministry of Health, Italian Association for Cancer Research, Fondazione Cariplo, National Cancer Institute **Country**: Italy **Setting**: hospital **Trial start date**: September 2005 **Completion of follow-up**: June 2018 **Trial registration number**: NCT02837809 **Corresponding author's name**: Ugo Pastorino **Institution**: IRCCS Istituto Nazionale dei Tumori, Milan, Italy **Email**: ugo.pastorino@isitutotumori.mi.it
Notes	**Conflicts of interest**: nil declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation via centralised stratified randomisation using blocks of variable size. Stratification based on reference centre, age (up to 65 years or older), duration of smoking (more or less than 40 years)
Allocation concealment (selection bias)	Low risk	Allocation concealment via centralised system
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded for the primary outcome of lung cancer-related mortality. It should be noted there was no review panel for lung cancer-related mortality.
Incomplete outcome data (attrition bias) All outcomes	Low risk	216 participants withdrew from intervention arms. Cause of death was missing in 3 cases (1 annual arm, 2 biennial arm), intention-to-treat analysis was applied
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	High risk	Initial recruitment commenced in September 2005 with only two arms, annual and biennial screwing with LDCT. 653 participants were recruited to these arms prior to approval in December 2005 and commencement of a control no-screening arm. 90% in the control were current smokers compared with 69% in the intervention group

Wille 2016

Study characteristics	
Methods	**Trial design**: phase 3 randomised control trial **Duration of follow-up**: At least 5 years **Number of trial locations**: 1
Participants	**Baseline characteristics** **Number of participants**: LDCT arm (2052); control arm (2052) **Age** • LDCT arm: 49 years old (8), 50-54 years old (586), 55-59 years old (676), 60-64 years old (604), 65-69 years old (169),70-74 years old (9) • Control arm: 49 years old (6), 50-54 years old (586), 55-59 years old (699), 60-64 years old (571), 65-69 years old (184),70-74 years old (6) **Sex**: LDCT arm (1147 males, 905 females); control arm (1120 males, 932 females) **Smoking status**: LDCT arm (1545 current, 507 former); control (1579 current, 473 former) **Performance status**: not published **Ethnicity/race**: not published **Environmental exposures**: not published **Inclusion criteria** • Men and women • Aged 50-70 years old • Without lung cancer-related symptoms • Current or former smokers (former smokers had to have quit after age of 50 and < 10 years ago) with ≥ 20 pack-year history of smoking • Able to climb 2 flights of stairs (36 steps) without pausing • FEV_1 ≥ 30% predicted **Exclusion criteria** • Body weight > 130 kg • Previous treatment for lung cancer, breast cancer, malignant melanoma, or hypernephroma • History of any other cancer within 5 years • Tuberculosis within 2 years • Any serious illness that would shorten life expectancy to < 10 years • Prior chest CT performed in the last year **Preintervention Investigations** Nil
Interventions	**Intervention characteristics** • Frequency of scanning: annual • LDCT setting: 120 kV, 40 mAs • Duration of screening: 5 years *Interpretation of scans* • Volumetric or size criteria: both • Use of volumetry software: yes

Wille 2016 *(Continued)*

- Criteria for significance: nodules ≥ 5 mm without benign characteristics
- Prespecified protocol for nodule follow-up: yes

Comparison

- Description: no screening. Annual clinic review for spirometry and questionnaires

Outcomes

Primary outcome

- Lung cancer mortality reduction

Secondary outcome

- All-cause mortality in each arm
- Number of lung cancers in each arm
- 5-year survival after diagnosis
- Stage and histology of lung cancer at diagnosis
- Surgical resection rate
- Effect on smoking behaviour
- Frequency of false-positive diagnosis
- Psychosocial consequences
- Health economic evaluations

Identification

Sponsorship source: Danish Ministry of Interior and Health

Country: Denmark

Setting: University Hospital

Trial start date: October 2004

Completion of follow-up: April 2015

Trial registration number: NCT00496977

Corresponding author's name: Mathilde Wille

Institution: Nordsjaellands Hospital, Denmark

Email: mathilde.winkler@gmail.com

Notes

Conflicts of interest: nil disclosures

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation via computer programme using a block of 10
Allocation concealment (selection bias)	Low risk	Random allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were not blinded

Wille 2016 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	The trial was single-blinded; local death review board blinded to allocation arm when assessing mortality, however assessors were not blinded for other outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	29 participants lost to follow-up due to emigration (15 in screening group) at first screening and 34 patients lost to follow-up due to emigration (20 in screening group, 14 in control group) < 1% participants lost to follow-up (34 of 4104) 2052 in each arm = 4104 in total trials
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	Minimal deviations. There were minor differences in baseline characteristics of participants with a lower mean FER in the LDCT group by 0.01, although no significant difference in the FEV_1. There were also more participants with > 35 pack-year smoking history in the LDCT group compared with control (45% versus 42%).

CT: computed tomography; CXR: chest x-ray; FER: forced expiratory ratio; FEV_1: forced expiratory volume in 1 second; LDCT: low-dose computed tomography; NIHR: National Institute for Health and Care Excellence; RCT: randomised controlled trial

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bradley 2021	Irrelevant intervention - lung health check versus usual care
Brodersen 2014	Irrelevant trial design
Dawson 2020	Irrelevant trial design
de-Torres 2021	Duplicate
Favre 2003	Irrelevant trial design
Fink 2012	Irrelevant trial design
Garg 2002	Irrelevant outcomes - feasibility of conducting a RCT for lung cancer screening among subjects with varying degrees of lung cancer risk
Goulart 2013	Irrelevant trial design
Guldbrandt 2015	Irrelevant patient population
Hassannezhad 2018	Irrelevant trial design
Henschke 2000	Irrelevant trial design
Henschke 2002	Irrelevant trial design
Henschke 2015	Irrelevant trial design

Study	Reason for exclusion
Horeweg 2013	Irrelevant trial design
ISRCTN42704678	Irrelevant intervention - lung health check versus usual care
Kramer 2011	Irrelevant trial design
Kulaga 2007	Irrelevant trial design
Marcus 2006	Irrelevant intervention - sputum cytology and CXR versus usual care
NCT02431962	Irrelevant trial design
Park 2022	Irrelevant outcome - to evaluate the effects of computer-aided diagnosis (CAD) on inter-reader agreement in Lung Imaging Reporting and Data System (Lung-RADS) categorisation
Robbins 2019	Irrelevant trial design
Schabath 2019	Irrelevant trial design
Schreuder 2021	Irrelevant trial design
Spiro 2019	Irrelevant intervention - sputum cytology and cytometry versus usual care
Strauss 2012	Irrelevant trial design
Strauss 2015	Irrelevant trial design
Sullivan 2019	Irrelevant intervention- serum biomarker versus usual care
Sullivan 2021	Irrelevant intervention - serum biomarker versus usual care
Yang 2008	Irrelevant intervention - LDCT and serum biomarker versus usual care
Yip 2013	Irrelevant trial design

CXR: chest x-ray; LDCT: low-dose computed tomography; RCT: randomised controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

Sagawa 2012

Study name	JECS study
Methods	**Trial design**: phase 3 RCT **Duration of follow-up**: not published **Number of trial locations**: 6 **Trial registration**: UMIN000005909
Participants	**Baseline characteristics** Number of participants: not published Age: not published

Sagawa 2012 *(Continued)*

	Sex: not published Smoking status: not published Performance status: not published Ethnicity: not published Environmental exposures: not published **Inclusion criteria** • People aged 50-64 years old when registering • People whose smoking history is < 30 pack years and never-smokers • People who received a lung cancer screening using CXR in previous year • People who provided informed consent to participate in this trial **Exclusion criteria** • People with a history of lung cancer • People under investigation/follow-up due to a suspicion of lung cancer • People with a history of malignant disease other than lung cancer within 5 years • People with a history of thoracic CT screening within 10 years • People in poor general condition, who are not expected to live for 5 years **Preintervention investigations** • Nil although as per inclusion criteria, participants received screening with CXR in previous year
Interventions	**Intervention characteristics** • Frequency of scanning: LDCT at baseline and in 5 years with CXR annually encouraged in other years • LDCT setting: not published • Duration of screening: 10 years *Interpretation of scans* • Volumetric or size criteria: bot published • Use of computer-assisted diagnostics: not published • Criteria for significance: as per the LDCT lung cancer screening guidelines for pulmonary nodule management by the Japanese Society of CT screening • Prespecified protocol for nodule follow-up: yes **Comparison** • Description: baseline CXR with annual CXR encouraged subsequently
Outcomes	**Primary outcome** • Sensitivity and specificity of screening modality for lung cancer between CT and CXR performed in first year of trial **Secondary outcomes** • Distribution of stages of lung cancer • Diameter of lung cancers • Rate of advanced lung cancers • Potential risks of screening- surgical resections, needle aspiration cytology or bronchoscopy for benign nodules • Mortality

Sagawa 2012 *(Continued)*

Starting date	2010
Contact information	Motoyasu Sagawa sagawam@tohoku-mpu.ac.jp
Notes	**Conflicts of interest**: nil disclosed

Yang 2018

Study name	AME Thoracic Surgery Collaborative Group
Methods	**Trial design**: phase 3 RCT **Duration of follow-up**: not published **Number of trial locations**: 1 **Trial registration**: not reported

Participants	**Baseline characteristics**
	Number of participants: LDCT arm (3512); control arm (3145)
	Age: mean age LDCT arm (60 years old); control arm (60 years old)
	Sex: LDCT arm (1625 males, 1887 females); control arm (1489 males, 1656 females)
	Smoking status: LDCT arm (729 current, 246 former, 831 passive); control arm (701 current, 202 former, 745 passive)
	Performance status: not published
	Ethnicity: not published
	Environmental exposures: LDCT arm (2144 cooking oil fumes, 34 asbestos, 248 dust, 57 radiation exposure); control arm (1924 cooking oil fumes, 24 asbestos, 212 dust, 47 radiation exposure)
	Inclusion criteria
	• Asymptomatic residents in selected housing estates
	• Age 45-70 years old
	• At least one of the following high-risk factors
	  ◦ Current or former smokers who had a history of ≥ 20 pack years, no more than 15 years since quitting
	  ◦ Cancer history of any kind in close family members
	  ◦ Cancer history of any kind for the participant
	  ◦ Occupational exposure to carcinogenic agents (asbestos, dust, or radiation)
	  ◦ Long history of passive smoking (> 2 hours every day in homes or indoor workplaces for at least 10 years)
	  ◦ Long-term exposure to cooking oil fumes (history of stir frying, frying, or deep frying > 50 dish years)
	Exclusion criteria
	• Previous diagnosis of lung cancer
	• Performance status score > 2
	• CT scan of chest within 12 months or had a diagnosis of any other cancer (including lung cancer) within the past 5 years

Yang 2018 *(Continued)*

	Preintervention investigations • Nil
Interventions	**Intervention characteristics** • Frequency of scanning: biennial • LDCT setting: 140 kVP, 40 mA • Duration of screening: 3 rounds of screening (6 years) *Interpretation of scans* • Volumetric or size criteria: both • Use of computer-assisted diagnostics: not specified • Criteria for significance: any non-calcified nodule or masses with longest diameter ≥ 4 mm • Prespecified protocol for nodule follow-up: yes **Comparison** • Description: no screening
Outcomes	**Primary outcome** • Efficiency of LDCT in lung cancer detection in asymptomatic high-risk population **Secondary outcome** • Lung cancer-specific mortality
Starting date	2013
Contact information	Baohui Han; xkyyhan@gmail.com
Notes	**Conflicts of interest**: nil disclosed

CT: computed tomography; CXR: chest x-ray; LDCT: low-dose computed tomography; RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. Primary outcome: lung cancer-related mortality

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Lung cancer-related mortality - planned time points	8	91122	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.72, 0.87]
1.2 Lung cancer-related mortality - planned time points	3		Hazard Ratio (IV, Random, 95% CI)	Subtotals only
1.2.1 8 to 10 years	3	10606	Hazard Ratio (IV, Random, 95% CI)	0.93 [0.72, 1.19]
1.3 Lung cancer-related mortality at different follow-up time points (including unplanned)	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3.1 5 to 6 years	4	27263	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.64, 1.24]
1.3.2 > 6 to 8 years	3	73211	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.69, 0.86]
1.3.3 > 8 to 10 years	6	33700	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.69, 0.90]
1.3.4 > 10 years	3	72447	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.75, 0.98]
1.4 Lung cancer-related mortality by screening arm - planned time points	8	91122	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.72, 0.87]
1.4.1 usual care	7	37668	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.69, 0.88]
1.4.2 CXR	1	53454	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.70, 0.92]
1.5 Lung cancer-related mortality – by time postscreening cessation (including unplanned time points)	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.5.1 0 to 1 year	4	28044	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.61, 0.94]
1.5.2 2 to 4.5 years	5	79063	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.72, 0.93]
1.5.3 5 to 7 years	4	27067	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.67, 0.90]
1.5.4 > 7 to 10 years	2	56658	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.83, 1.01]
1.6 Lung cancer-related mortality by screening interval - planned time points	8	91122	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.72, 0.87]
1.6.1 annual - 1 screen	1	3968	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.41, 1.03]
1.6.2 annual - 3 screens	1	53454	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.70, 0.92]
1.6.3 annual - 4 screens	1	3206	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.48, 1.04]
1.6.4 annual - 5 screens	3	10606	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.73, 1.18]

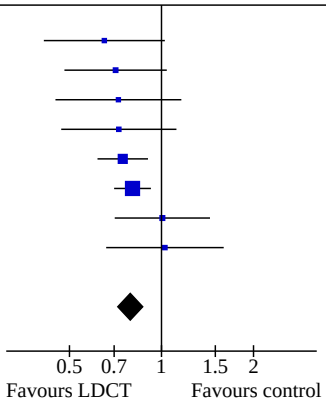
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.6.5 annual - 7 screens	1	2052	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.37, 1.28]
1.6.6 biennial - 4 screens	1	2047	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.42, 1.40]
1.6.7 incremental - interval 4 screens	1	15789	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.62, 0.90]
1.7 Lung cancer-related mortality by sex - planned time points	3	9944	Hazard Ratio (IV, Random, 95% CI)	0.80 [0.55, 1.17]
1.7.1 females	3	4286	Hazard Ratio (IV, Random, 95% CI)	0.73 [0.34, 1.56]
1.7.2 males	2	5658	Hazard Ratio (IV, Random, 95% CI)	0.76 [0.52, 1.12]
1.8 Lung cancer-related mortality by sex - planned time points	5	79798	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.73, 0.89]
1.8.1 females	4	26965	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.59, 0.86]
1.8.2 males	5	52833	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.76, 0.95]
1.9 Lung cancer-related mortality by age - planned time points	1	56452	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.54, 0.95]
1.9.1 < 65 years old	1	39234	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.70, 0.97]
1.9.2 ≥ 65 years old	1	17218	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.52, 0.74]
1.10 Lung cancer related to smoking - latest time point (including unplanned)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.10.1 current smokers at 6.5 years - planned	1	25760	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.70, 0.95]
1.10.2 former smokers at 6.5 years - planned	1	27692	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.74, 1.11]
1.10.3 current smokers at 12.3 years - unplanned	1	25760	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.81, 0.98]
1.10.4 former smokers at 12.3 years - unplanned	1	27692	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.88, 1.15]
1.10.5 < 35 pack-history	1	2148	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.55, 2.90]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.10.6 ≥ 35 pack-history	1	1955	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.54, 1.54]
1.11 Lung cancer-related mortality by geography - planned time points	8	91122	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.72, 0.87]
1.11.1 Europe	7	37668	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.69, 0.88]
1.11.2 USA	1	53454	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.70, 0.92]
1.12 Nodule management algorithm - planned follow-up time points	8	91122	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.72, 0.87]
1.12.1 yes	6	35218	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.66, 0.86]
1.12.2 no	2	55904	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.70, 1.01]
1.13 Nodule management criteria - planned follow-up time points	8	91122	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.72, 0.87]
1.13.1 diameter	3	59110	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.72, 0.92]
1.13.2 volume	2	19888	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.62, 0.88]
1.13.3 diameter and volume	3	12124	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.60, 1.04]

Analysis 1.1. Comparison 1: Primary outcome: lung cancer-related mortality, Outcome 1: Lung cancer-related mortality - planned time points

Study or Subgroup	LDCT Events	LDCT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Field 2021	30	1987	46	1981	4.2%	0.65 [0.41 , 1.03]
Paci 2017	43	1613	60	1593	5.9%	0.71 [0.48 , 1.04]
Becker 2020	29	2029	40	2023	3.9%	0.72 [0.45 , 1.16]
Pastorino 2012	40	2376	40	1723	4.7%	0.73 [0.47 , 1.12]
De Koning 2020	181	7900	242	7889	24.3%	0.75 [0.62 , 0.90]
Aberle 2011	356	26722	443	26732	45.7%	0.80 [0.70 , 0.92]
Infante 2015	59	1264	55	1186	6.8%	1.01 [0.70 , 1.44]
Wille 2016	39	2052	38	2052	4.5%	1.03 [0.66 , 1.60]
Total (95% CI)		**45943**		**45179**	**100.0%**	**0.79 [0.72 , 0.87]**
Total events:	777		964			

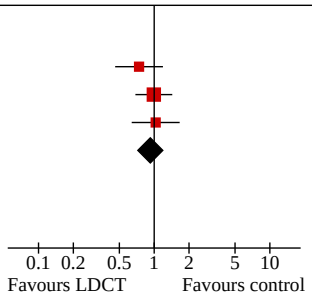
Heterogeneity: Tau² = 0.00; Chi² = 4.79, df = 7 (P = 0.69); I² = 0%
Test for overall effect: Z = 4.92 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Primary outcome: lung cancer-related mortality, Outcome 2: Lung cancer-related mortality - planned time points

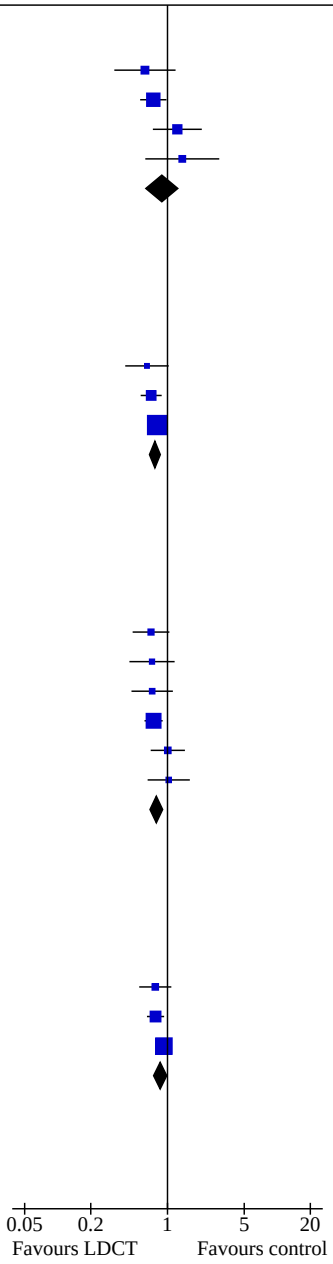
Study or Subgroup	log[Hazard Ratio]	SE	LDTS Total	Control Total	Weight	Hazard Ratio IV, Random, 95% CI
1.2.1 8 to 10 years						
Becker 2020	-0.3013	0.2425	2029	2023	27.2%	0.74 [0.46 , 1.19]
Infante 2015	-0.0071	0.1872	1264	1186	45.7%	0.99 [0.69 , 1.43]
Wille 2016	0.0296	0.2435	2052	2052	27.0%	1.03 [0.64 , 1.66]
Subtotal (95% CI)			**5345**	**5261**	**100.0%**	**0.93 [0.72 , 1.19]**

Heterogeneity: Tau² = 0.00; Chi² = 1.19, df = 2 (P = 0.55); I² = 0%
Test for overall effect: Z = 0.61 (P = 0.54)



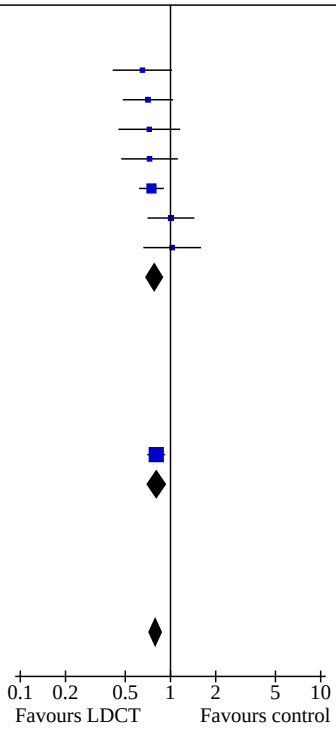
Analysis 1.3. Comparison 1: Primary outcome: lung cancer-related mortality, Outcome 3: Lung cancer-related mortality at different follow-up time points (including unplanned)

Study or Subgroup	LDCT Events	LDCT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 5 to 6 years						
Becker 2020	15	2029	24	2023	18.7%	0.62 [0.33 , 1.18]
De Koning 2020	87	7900	117	7889	42.3%	0.74 [0.56 , 0.98]
Gohagan 2005	32	1660	26	1658	24.8%	1.23 [0.74 , 2.05]
Wille 2016	15	2052	11	2052	14.2%	1.36 [0.63 , 2.96]
Subtotal (95% CI)		**13641**		**13622**	**100.0%**	**0.89 [0.64 , 1.24]**
Total events:	149		178			
Heterogeneity: Tau² = 0.05; Chi² = 5.21, df = 3 (P = 0.16); I² = 42%						
Test for overall effect: Z = 0.70 (P = 0.49)						
1.3.2 > 6 to 8 years						
Field 2021	30	1987	46	1981	6.2%	0.65 [0.41 , 1.03]
De Koning 2020	133	7900	187	7889	26.6%	0.71 [0.57 , 0.89]
Aberle 2011	356	26722	443	26732	67.2%	0.80 [0.70 , 0.92]
Subtotal (95% CI)		**36609**		**36602**	**100.0%**	**0.77 [0.69 , 0.86]**
Total events:	519		676			
Heterogeneity: Tau² = 0.00; Chi² = 1.42, df = 2 (P = 0.49); I² = 0%						
Test for overall effect: Z = 4.56 (P < 0.00001)						
1.3.3 > 8 to 10 years						
Paci 2017	43	1613	60	1593	11.8%	0.71 [0.48 , 1.04]
Becker 2020	29	2029	40	2023	7.8%	0.72 [0.45 , 1.16]
Pastorino 2012	40	2376	40	1723	9.3%	0.73 [0.47 , 1.12]
De Koning 2020	181	7900	242	7889	48.5%	0.75 [0.62 , 0.90]
Infante 2015	59	1264	55	1186	13.6%	1.01 [0.70 , 1.44]
Wille 2016	39	2052	38	2052	8.9%	1.03 [0.66 , 1.60]
Subtotal (95% CI)		**17234**		**16466**	**100.0%**	**0.79 [0.69 , 0.90]**
Total events:	391		475			
Heterogeneity: Tau² = 0.00; Chi² = 4.03, df = 5 (P = 0.55); I² = 0%						
Test for overall effect: Z = 3.47 (P = 0.0005)						
1.3.4 > 10 years						
Paci 2017	58	1613	74	1593	13.4%	0.77 [0.55 , 1.08]
De Koning 2020	205	7900	263	7889	31.3%	0.78 [0.65 , 0.93]
Aberle 2011	1147	26722	1236	26730	55.4%	0.93 [0.86 , 1.00]
Subtotal (95% CI)		**36235**		**36212**	**100.0%**	**0.86 [0.75 , 0.98]**
Total events:	1410		1573			
Heterogeneity: Tau² = 0.01; Chi² = 3.85, df = 2 (P = 0.15); I² = 48%						
Test for overall effect: Z = 2.20 (P = 0.03)						



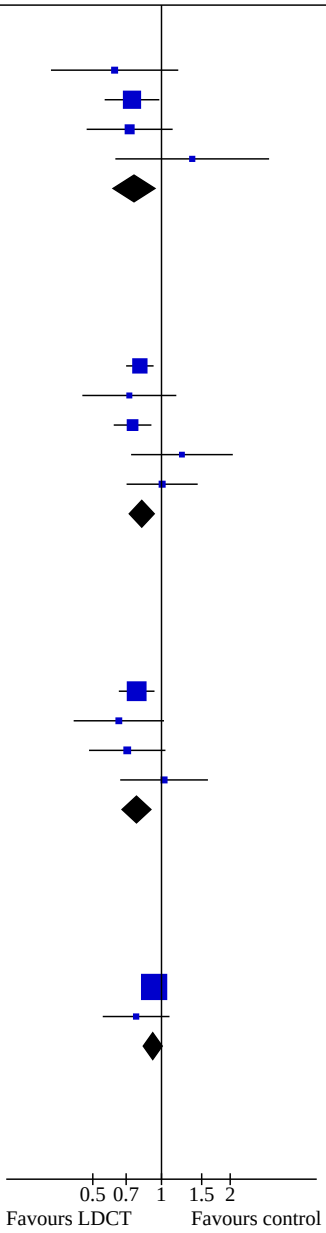
Analysis 1.4. Comparison 1: Primary outcome: lung cancer-related mortality, Outcome 4: Lung cancer-related mortality by screening arm - planned time points

Study or Subgroup	LDCT Events	LDCT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 usual care						
Field 2021	30	1987	46	1981	4.2%	0.65 [0.41 , 1.03]
Paci 2017	43	1613	60	1593	5.9%	0.71 [0.48 , 1.04]
Becker 2020	29	2029	40	2023	3.9%	0.72 [0.45 , 1.16]
Pastorino 2012	40	2376	40	1723	4.7%	0.73 [0.47 , 1.12]
De Koning 2020	181	7900	242	7889	24.3%	0.75 [0.62 , 0.90]
Infante 2015	59	1264	55	1186	6.8%	1.01 [0.70 , 1.44]
Wille 2016	39	2052	38	2052	4.5%	1.03 [0.66 , 1.60]
Subtotal (95% CI)		**19221**		**18447**	**54.3%**	**0.78 [0.69 , 0.88]**
Total events:	421		521			
Heterogeneity: Tau² = 0.00; Chi² = 4.68, df = 6 (P = 0.59); I² = 0%						
Test for overall effect: Z = 3.85 (P = 0.0001)						
1.4.2 CXR						
Aberle 2011	356	26722	443	26732	45.7%	0.80 [0.70 , 0.92]
Subtotal (95% CI)		**26722**		**26732**	**45.7%**	**0.80 [0.70 , 0.92]**
Total events:	356		443			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.09 (P = 0.002)						
Total (95% CI)		**45943**		**45179**	**100.0%**	**0.79 [0.72 , 0.87]**
Total events:	777		964			
Heterogeneity: Tau² = 0.00; Chi² = 4.79, df = 7 (P = 0.69); I² = 0%						
Test for overall effect: Z = 4.92 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.11, df = 1 (P = 0.74), I² = 0%						



Analysis 1.5. Comparison 1: Primary outcome: lung cancer-related mortality, Outcome 5: Lung cancer-related mortality – by time postscreening cessation (including unplanned time points)

Study or Subgroup	LDCT Events	LDCT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 0 to 1 year						
Becker 2020	15	2029	24	2023	10.8%	0.62 [0.33 , 1.18]
De Koning 2020	87	7900	117	7889	58.3%	0.74 [0.56 , 0.98]
Pastorino 2012	40	2376	40	1723	23.6%	0.73 [0.47 , 1.12]
Wille 2016	15	2052	11	2052	7.4%	1.36 [0.63 , 2.96]
Subtotal (95% CI)		**14357**		**13687**	**100.0%**	**0.76 [0.61 , 0.94]**
Total events:	157		192			
Heterogeneity: Tau² = 0.00; Chi² = 2.62, df = 3 (P = 0.45); I² = 0%						
Test for overall effect: Z = 2.58 (P = 0.010)						
1.5.2 2 to 4.5 years						
Aberle 2011	356	26722	443	26732	46.0%	0.80 [0.70 , 0.92]
Becker 2020	29	2029	40	2023	6.6%	0.72 [0.45 , 1.16]
De Koning 2020	181	7900	242	7889	30.8%	0.75 [0.62 , 0.90]
Gohagan 2005	32	1660	26	1658	5.7%	1.23 [0.74 , 2.05]
Infante 2015	59	1264	55	1186	11.0%	1.01 [0.70 , 1.44]
Subtotal (95% CI)		**39575**		**39488**	**100.0%**	**0.82 [0.72 , 0.93]**
Total events:	657		806			
Heterogeneity: Tau² = 0.00; Chi² = 4.88, df = 4 (P = 0.30); I² = 18%						
Test for overall effect: Z = 3.11 (P = 0.002)						
1.5.3 5 to 7 years						
De Koning 2020	205	7900	263	7889	65.0%	0.78 [0.65 , 0.93]
Field 2021	30	1987	46	1981	10.1%	0.65 [0.41 , 1.03]
Paci 2017	43	1613	60	1593	14.2%	0.71 [0.48 , 1.04]
Wille 2016	39	2052	38	2052	10.7%	1.03 [0.66 , 1.60]
Subtotal (95% CI)		**13552**		**13515**	**100.0%**	**0.78 [0.67 , 0.90]**
Total events:	317		407			
Heterogeneity: Tau² = 0.00; Chi² = 2.33, df = 3 (P = 0.51); I² = 0%						
Test for overall effect: Z = 3.41 (P = 0.0006)						
1.5.4 > 7 to 10 years						
Aberle 2011	1147	26722	1236	26730	92.3%	0.93 [0.86 , 1.00]
Paci 2017	58	1613	74	1593	7.7%	0.77 [0.55 , 1.08]
Subtotal (95% CI)		**28335**		**28323**	**100.0%**	**0.92 [0.83 , 1.01]**
Total events:	1205		1310			
Heterogeneity: Tau² = 0.00; Chi² = 1.06, df = 1 (P = 0.30); I² = 6%						
Test for overall effect: Z = 1.82 (P = 0.07)						



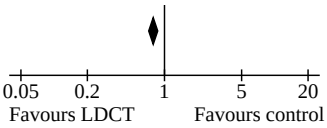
Analysis 1.6. Comparison 1: Primary outcome: lung cancer-related mortality, Outcome 6: Lung cancer-related mortality by screening interval - planned time points

Study or Subgroup	LDCT Events	LDCT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 annual - 1 screen						
Field 2021	30	1987	46	1981	4.2%	0.65 [0.41 , 1.03]
Subtotal (95% CI)		**1987**		**1981**	**4.2%**	**0.65 [0.41 , 1.03]**
Total events:	30		46			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.85 (P = 0.06)						
1.6.2 annual - 3 screens						
Aberle 2011	356	26722	443	26732	45.7%	0.80 [0.70 , 0.92]
Subtotal (95% CI)		**26722**		**26732**	**45.7%**	**0.80 [0.70 , 0.92]**
Total events:	356		443			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.09 (P = 0.002)						
1.6.3 annual - 4 screens						
Paci 2017	43	1613	60	1593	5.9%	0.71 [0.48 , 1.04]
Subtotal (95% CI)		**1613**		**1593**	**5.9%**	**0.71 [0.48 , 1.04]**
Total events:	43		60			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.76 (P = 0.08)						
1.6.4 annual - 5 screens						
Becker 2020	29	2029	40	2023	3.9%	0.72 [0.45 , 1.16]
Infante 2015	59	1264	55	1186	6.8%	1.01 [0.70 , 1.44]
Wille 2016	39	2052	38	2052	4.5%	1.03 [0.66 , 1.60]
Subtotal (95% CI)		**5345**		**5261**	**15.2%**	**0.93 [0.73 , 1.18]**
Total events:	127		133			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.46$, df = 2 (P = 0.48); $I^2 = 0\%$						
Test for overall effect: Z = 0.59 (P = 0.55)						
1.6.5 annual - 7 screens						
Pastorino 2012	19	1190	20	862	2.3%	0.69 [0.37 , 1.28]
Subtotal (95% CI)		**1190**		**862**	**2.3%**	**0.69 [0.37 , 1.28]**
Total events:	19		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.18 (P = 0.24)						
1.6.6 biennial - 4 screens						
Pastorino 2012	21	1186	20	861	2.4%	0.76 [0.42 , 1.40]
Subtotal (95% CI)		**1186**		**861**	**2.4%**	**0.76 [0.42 , 1.40]**
Total events:	21		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.88 (P = 0.38)						
1.6.7 incremental - interval 4 screens						
De Koning 2020	181	7900	242	7889	24.3%	0.75 [0.62 , 0.90]
Subtotal (95% CI)		**7900**		**7889**	**24.3%**	**0.75 [0.62 , 0.90]**
Total events:	181		242			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.01 (P = 0.003)						
Total (95% CI)		**45943**		**45179**	**100.0%**	**0.79 [0.72 , 0.87]**
Total events:	777		964			

Analysis 1.6. (Continued)

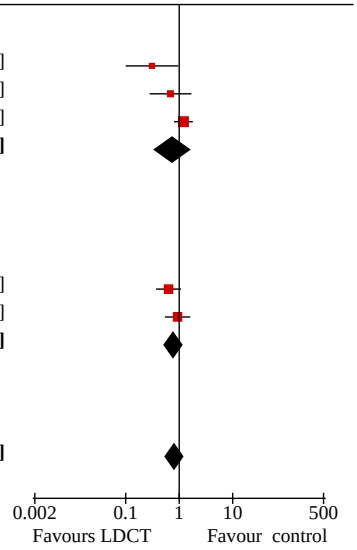
Total (95% CI)	**45943**	**45179**	**100.0%**	**0.79 [0.72 , 0.87]**	
Total events:	777	964			

Heterogeneity: Tau² = 0.00; Chi² = 4.84, df = 8 (P = 0.77); I² = 0%
Test for overall effect: Z = 4.92 (P < 0.00001)
Test for subgroup differences: Chi² = 3.38, df = 6 (P = 0.76), I² = 0%



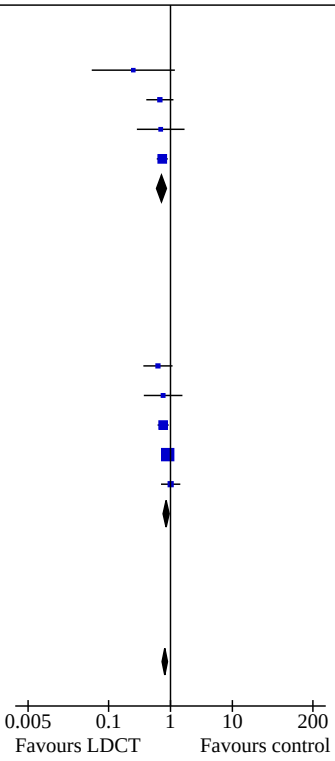
Analysis 1.7. Comparison 1: Primary outcome: lung cancer-related mortality, Outcome 7: Lung cancer-related mortality by sex - planned time points

Study or Subgroup	log[Hazard Ratio]	SE	LDCT Total	Control Total	Weight	Hazard Ratio IV, Random, 95% CI
1.7.1 females						
Becker 2020	-1.1717	0.577	714	716	9.0%	0.31 [0.10 , 0.96]
Field 2021	-0.3741	0.4586	499	520	12.8%	0.69 [0.28 , 1.69]
Wille 2016	0.1823	0.2069	905	932	30.4%	1.20 [0.80 , 1.80]
Subtotal (95% CI)			**2118**	**2168**	**52.2%**	**0.73 [0.34 , 1.56]**
Heterogeneity: Tau² = 0.28; Chi² = 5.53, df = 2 (P = 0.06); I² = 64%						
Test for overall effect: Z = 0.81 (P = 0.42)						
1.7.2 males						
Field 2021	-0.4586	0.2733	1529	1507	24.1%	0.63 [0.37 , 1.08]
Becker 2020	-0.07	0.2787	1315	1307	23.7%	0.93 [0.54 , 1.61]
Subtotal (95% CI)			**2844**	**2814**	**47.8%**	**0.76 [0.52 , 1.12]**
Heterogeneity: Tau² = 0.00; Chi² = 0.99, df = 1 (P = 0.32); I² = 0%						
Test for overall effect: Z = 1.37 (P = 0.17)						
Total (95% CI)			**4962**	**4982**	**100.0%**	**0.80 [0.55 , 1.17]**
Heterogeneity: Tau² = 0.08; Chi² = 7.31, df = 4 (P = 0.12); I² = 45%						
Test for overall effect: Z = 1.17 (P = 0.24)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.92), I² = 0%						



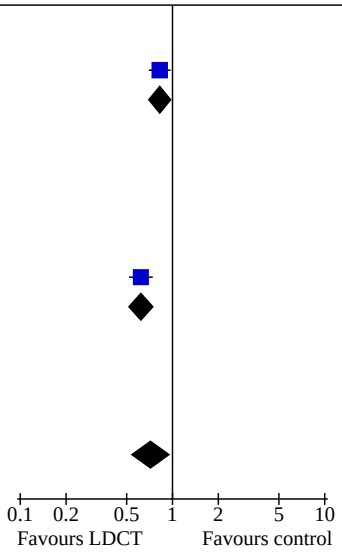
Analysis 1.8. Comparison 1: Primary outcome: lung cancer-related mortality, Outcome 8: Lung cancer-related mortality by sex - planned time points

Study or Subgroup	LDCT Events	LDCT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 females						
Becker 2020	2	714	8	716	0.4%	0.25 [0.05 , 1.18]
De Koning 2020	25	1317	36	1277	3.8%	0.67 [0.41 , 1.12]
Field 2021	8	499	12	520	1.2%	0.69 [0.29 , 1.69]
Aberle 2011	158	10953	215	10969	22.1%	0.74 [0.60 , 0.90]
Subtotal (95% CI)		**13483**		**13482**	**27.6%**	**0.71 [0.59 , 0.86]**
Total events:	193		271			
Heterogeneity: Tau² = 0.00; Chi² = 1.90, df = 3 (P = 0.59); I² = 0%						
Test for overall effect: Z = 3.59 (P = 0.0003)						
1.8.2 males						
Field 2021	21	1529	33	1507	3.3%	0.63 [0.36 , 1.08]
Becker 2020	13	1315	17	1307	1.9%	0.76 [0.37 , 1.56]
De Koning 2020	156	6583	206	6612	21.8%	0.76 [0.62 , 0.93]
Aberle 2011	311	15769	345	15761	37.9%	0.90 [0.77 , 1.05]
Infante 2015	59	1264	55	1186	7.5%	1.01 [0.70 , 1.44]
Subtotal (95% CI)		**26460**		**26373**	**72.4%**	**0.85 [0.76 , 0.95]**
Total events:	560		656			
Heterogeneity: Tau² = 0.00; Chi² = 3.85, df = 4 (P = 0.43); I² = 0%						
Test for overall effect: Z = 2.86 (P = 0.004)						
Total (95% CI)		**39943**		**39855**	**100.0%**	**0.81 [0.73 , 0.89]**
Total events:	753		927			
Heterogeneity: Tau² = 0.00; Chi² = 8.24, df = 8 (P = 0.41); I² = 3%						
Test for overall effect: Z = 4.20 (P < 0.0001)						
Test for subgroup differences: Chi² = 2.49, df = 1 (P = 0.11), I² = 59.9%						



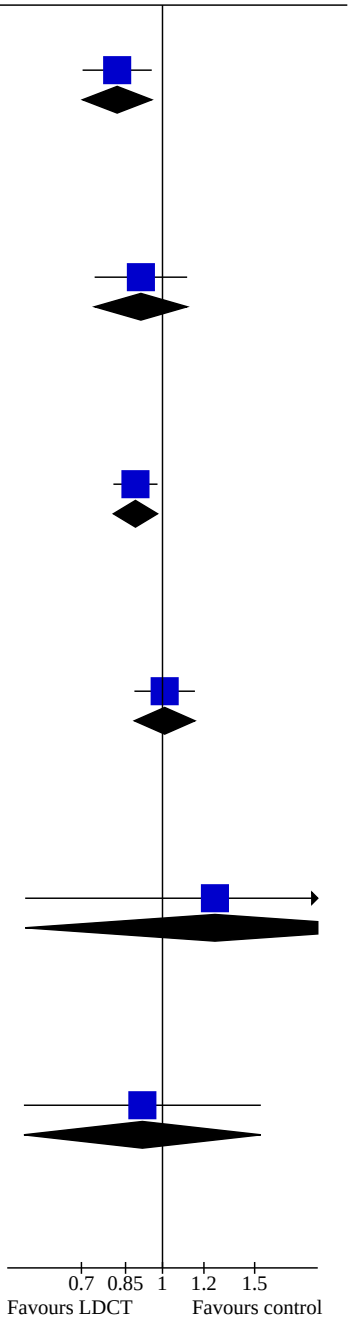
Analysis 1.9. Comparison 1: Primary outcome: lung cancer-related mortality, Outcome 9: Lung cancer-related mortality by age - planned time points

Study or Subgroup	LDCT Events	LDCT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.9.1 < 65 years old						
Aberle 2011	253	19612	307	19622	50.8%	0.82 [0.70 , 0.97]
Subtotal (95% CI)		**19612**		**19622**	**50.8%**	**0.82 [0.70 , 0.97]**
Total events:	253		307			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.29 (P = 0.02)						
1.9.2 ≥ 65 years old						
Aberle 2011	216	10110	245	7108	49.2%	0.62 [0.52 , 0.74]
Subtotal (95% CI)		**10110**		**7108**	**49.2%**	**0.62 [0.52 , 0.74]**
Total events:	216		245			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.20 (P < 0.00001)						
Total (95% CI)		**29722**		**26730**	**100.0%**	**0.72 [0.54 , 0.95]**
Total events:	469		552			
Heterogeneity: Tau² = 0.03; Chi² = 5.23, df = 1 (P = 0.02); I² = 81%						
Test for overall effect: Z = 2.34 (P = 0.02)						
Test for subgroup differences: Chi² = 5.23, df = 1 (P = 0.02), I² = 80.9%						



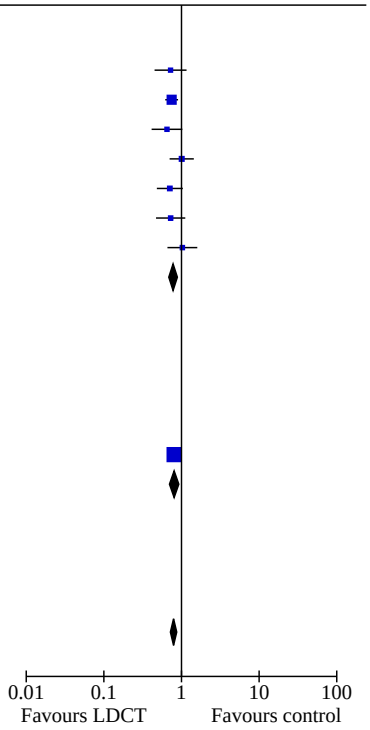
Analysis 1.10. Comparison 1: Primary outcome: lung cancer-related mortality, Outcome 10: Lung cancer related to smoking - latest time point (including unplanned)

Study or Subgroup	LDCT Events	LDCT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.10.1 current smokers at 6.5 years - planned						
Aberle 2011	294	12860	360	12900	100.0%	0.82 [0.70 , 0.95]
Subtotal (95% CI)		**12860**		**12900**	**100.0%**	**0.82 [0.70 , 0.95]**
Total events:	294		360			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.57 (P = 0.01)						
1.10.2 former smokers at 6.5 years - planned						
Aberle 2011	175	13862	192	13830	100.0%	0.91 [0.74 , 1.11]
Subtotal (95% CI)		**13862**		**13830**	**100.0%**	**0.91 [0.74 , 1.11]**
Total events:	175		192			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.92 (P = 0.36)						
1.10.3 current smokers at 12.3 years - unplanned						
Aberle 2011	724	12860	818	12900	100.0%	0.89 [0.81 , 0.98]
Subtotal (95% CI)		**12860**		**12900**	**100.0%**	**0.89 [0.81 , 0.98]**
Total events:	724		818			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.40 (P = 0.02)						
1.10.4 former smokers at 12.3 years - unplanned						
Aberle 2011	423	13862	418	13830	100.0%	1.01 [0.88 , 1.15]
Subtotal (95% CI)		**13862**		**13830**	**100.0%**	**1.01 [0.88 , 1.15]**
Total events:	423		418			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.14 (P = 0.89)						
1.10.5 < 35 pack-history						
Wille 2016	12	1048	10	1100	100.0%	1.26 [0.55 , 2.90]
Subtotal (95% CI)		**1048**		**1100**	**100.0%**	**1.26 [0.55 , 2.90]**
Total events:	12		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.54 (P = 0.59)						
1.10.6 ≥ 35 pack-history						
Wille 2016	27	1003	28	952	100.0%	0.92 [0.54 , 1.54]
Subtotal (95% CI)		**1003**		**952**	**100.0%**	**0.92 [0.54 , 1.54]**
Total events:	27		28			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.33 (P = 0.74)						
Test for subgroup differences: Chi^2 = 4.99, df = 5 (P = 0.42), I^2 = 0%						



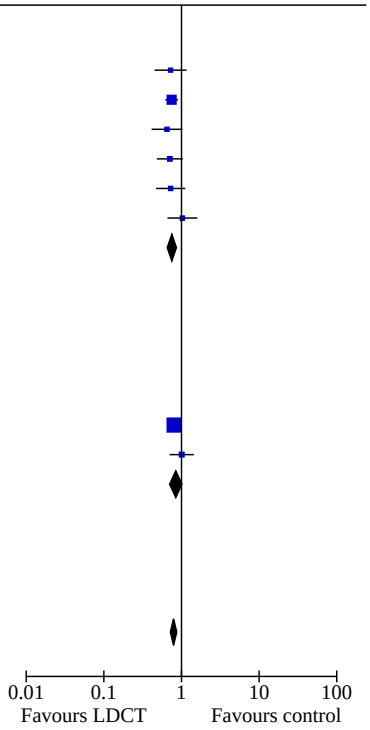
Analysis 1.11. Comparison 1: Primary outcome: lung cancer-related mortality, Outcome 11: Lung cancer-related mortality by geography - planned time points

Study or Subgroup	LDCT Events	LDCT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.11.1 Europe						
Becker 2020	29	2029	40	2023	3.9%	0.72 [0.45 , 1.16]
De Koning 2020	181	7900	242	7889	24.3%	0.75 [0.62 , 0.90]
Field 2021	30	1987	46	1981	4.2%	0.65 [0.41 , 1.03]
Infante 2015	59	1264	55	1186	6.8%	1.01 [0.70 , 1.44]
Paci 2017	43	1613	60	1593	5.9%	0.71 [0.48 , 1.04]
Pastorino 2012	40	2376	40	1723	4.7%	0.73 [0.47 , 1.12]
Wille 2016	39	2052	38	2052	4.5%	1.03 [0.66 , 1.60]
Subtotal (95% CI)		**19221**		**18447**	**54.3%**	**0.78 [0.69 , 0.88]**
Total events:	421		521			
Heterogeneity: Tau² = 0.00; Chi² = 4.68, df = 6 (P = 0.59); I² = 0%						
Test for overall effect: Z = 3.85 (P = 0.0001)						
1.11.2 USA						
Aberle 2011	356	26722	443	26732	45.7%	0.80 [0.70 , 0.92]
Subtotal (95% CI)		**26722**		**26732**	**45.7%**	**0.80 [0.70 , 0.92]**
Total events:	356		443			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.09 (P = 0.002)						
Total (95% CI)		**45943**		**45179**	**100.0%**	**0.79 [0.72 , 0.87]**
Total events:	777		964			
Heterogeneity: Tau² = 0.00; Chi² = 4.79, df = 7 (P = 0.69); I² = 0%						
Test for overall effect: Z = 4.92 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.11, df = 1 (P = 0.74), I² = 0%						

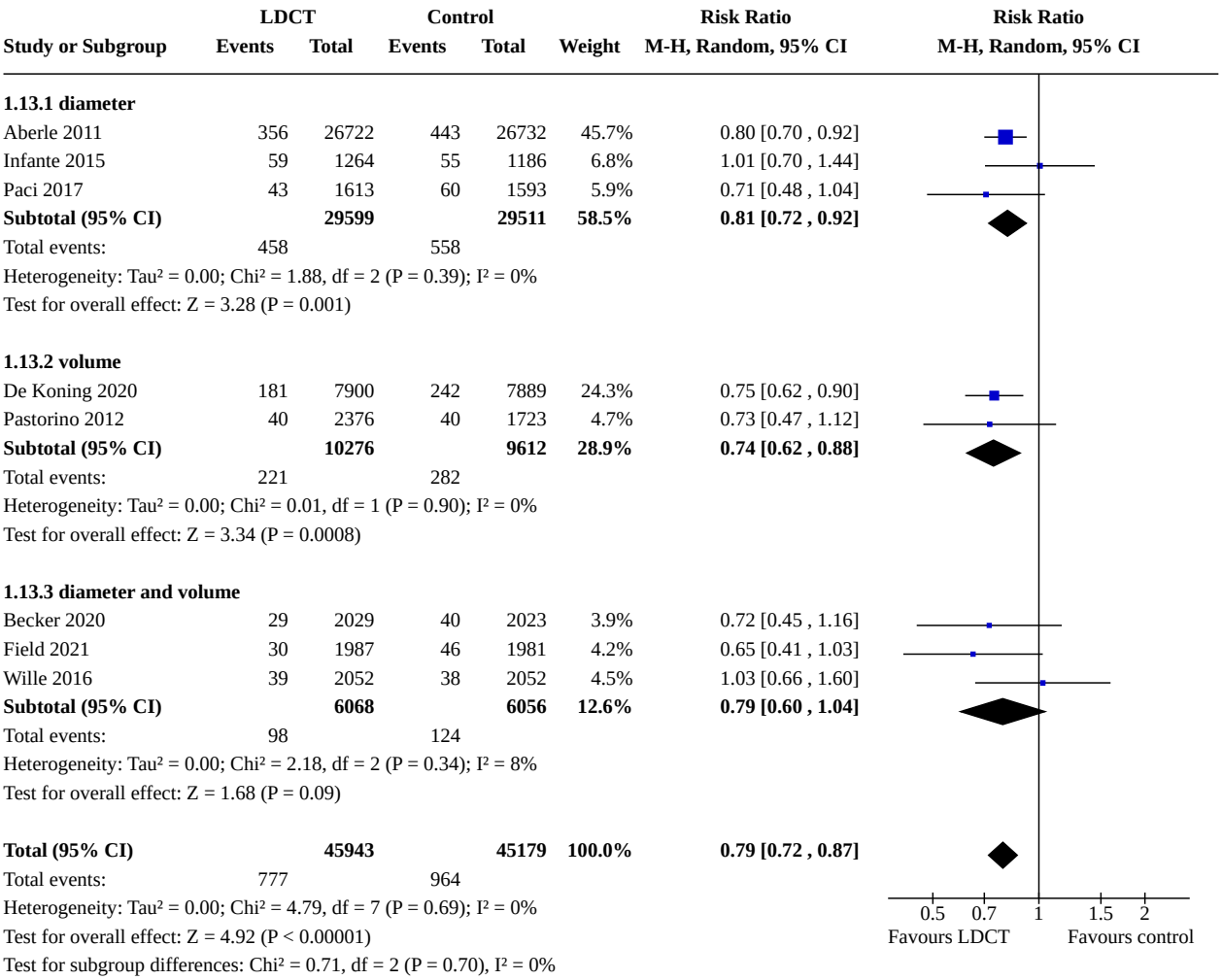


Analysis 1.12. Comparison 1: Primary outcome: lung cancer-related mortality, Outcome 12: Nodule management algorithm - planned follow-up time points

Study or Subgroup	LDCT Events	LDCT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.12.1 yes						
Becker 2020	29	2029	40	2023	3.9%	0.72 [0.45 , 1.16]
De Koning 2020	181	7900	242	7889	24.3%	0.75 [0.62 , 0.90]
Field 2021	30	1987	46	1981	4.2%	0.65 [0.41 , 1.03]
Paci 2017	43	1613	60	1593	5.9%	0.71 [0.48 , 1.04]
Pastorino 2012	40	2376	40	1723	4.7%	0.73 [0.47 , 1.12]
Wille 2016	39	2052	38	2052	4.5%	1.03 [0.66 , 1.60]
Subtotal (95% CI)		**17957**		**17261**	**47.4%**	**0.75 [0.66 , 0.86]**
Total events:	362		466			
Heterogeneity: Tau² = 0.00; Chi² = 2.44, df = 5 (P = 0.79); I² = 0%						
Test for overall effect: Z = 4.13 (P < 0.0001)						
1.12.2 no						
Aberle 2011	356	26722	443	26732	45.7%	0.80 [0.70 , 0.92]
Infante 2015	59	1264	55	1186	6.8%	1.01 [0.70 , 1.44]
Subtotal (95% CI)		**27986**		**27918**	**52.6%**	**0.84 [0.70 , 1.01]**
Total events:	415		498			
Heterogeneity: Tau² = 0.01; Chi² = 1.31, df = 1 (P = 0.25); I² = 24%						
Test for overall effect: Z = 1.82 (P = 0.07)						
Total (95% CI)		**45943**		**45179**	**100.0%**	**0.79 [0.72 , 0.87]**
Total events:	777		964			
Heterogeneity: Tau² = 0.00; Chi² = 4.79, df = 7 (P = 0.69); I² = 0%						
Test for overall effect: Z = 4.92 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.02, df = 1 (P = 0.31), I² = 2.2%						



Analysis 1.13. Comparison 1: Primary outcome: lung cancer-related mortality, Outcome 13: Nodule management criteria - planned follow-up time points



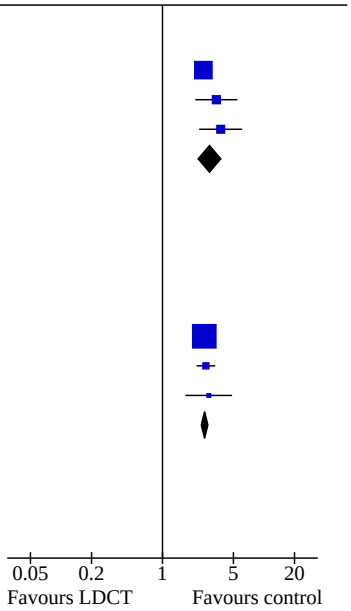
Comparison 2. Primary outcome: number of non-invasive and invasive tests - all time points

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Number of invasive tests	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1.1 at baseline	3	59222	Risk Ratio (M-H, Random, 95% CI)	2.90 [2.25, 3.75]
2.1.2 at follow-up	3	60003	Risk Ratio (M-H, Random, 95% CI)	2.60 [2.41, 2.80]
2.2 Non-invasive tests	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.2.1 at baseline	3	59222	Risk Ratio (M-H, Random, 95% CI)	3.28 [2.40, 4.48]
2.2.2 at follow-up	2	55905	Risk Ratio (M-H, Random, 95% CI)	3.56 [1.81, 7.01]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3 Number of invasive test for false positive	4	63323	Risk Ratio (M-H, Random, 95% CI)	3.84 [3.18, 4.64]
2.3.1 at baseline	1	3318	Risk Ratio (M-H, Random, 95% CI)	3.09 [1.57, 6.07]
2.3.2 at follow-up	3	60005	Risk Ratio (M-H, Random, 95% CI)	3.91 [3.21, 4.76]
2.4 Death postsurgery	2	409	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.24, 1.94]

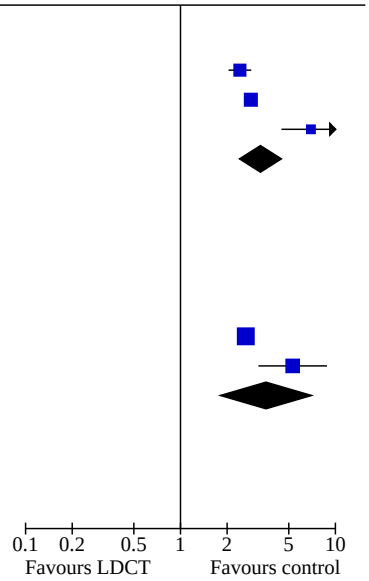
Analysis 2.1. Comparison 2: Primary outcome: number of non-invasive and invasive tests - all time points, Outcome 1: Number of invasive tests

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 at baseline						
Aberle 2011	926	26722	366	26732	59.8%	2.53 [2.25 , 2.85]
Infante 2015	76	1264	21	1186	20.4%	3.40 [2.11 , 5.47]
Gohagan 2005	75	1660	20	1658	19.7%	3.75 [2.30 , 6.10]
Subtotal (95% CI)		**29646**		**29576**	**100.0%**	**2.90 [2.25 , 3.75]**
Total events:	1077		407			
Heterogeneity: Tau² = 0.02; Chi² = 3.51, df = 2 (P = 0.17); I² = 43%						
Test for overall effect: Z = 8.13 (P < 0.00001)						
2.1.2 at follow-up						
Aberle 2011	2033	26722	788	26732	85.6%	2.58 [2.38 , 2.80]
Infante 2015	291	1264	102	1186	12.4%	2.68 [2.17 , 3.31]
Pastorino 2012	67	2376	17	1723	2.0%	2.86 [1.68 , 4.85]
Subtotal (95% CI)		**30362**		**29641**	**100.0%**	**2.60 [2.41 , 2.80]**
Total events:	2391		907			
Heterogeneity: Tau² = 0.00; Chi² = 0.23, df = 2 (P = 0.89); I² = 0%						
Test for overall effect: Z = 25.13 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.66, df = 1 (P = 0.41), I² = 0%						



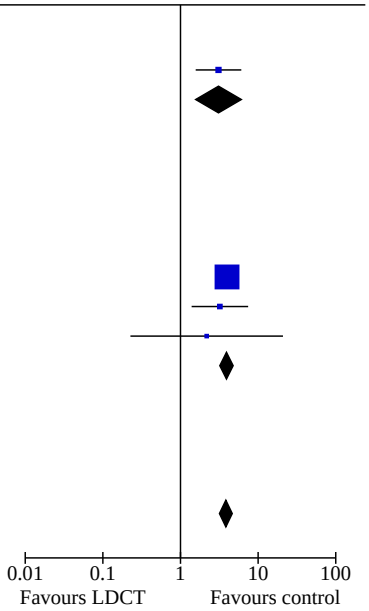
Analysis 2.2. Comparison 2: Primary outcome: number of non-invasive and invasive tests - all time points, Outcome 2: Non-invasive tests

Study or Subgroup	LDCT Events	LDCT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 at baseline						
Gohagan 2005	397	1660	164	1658	36.7%	2.42 [2.04 , 2.86]
Aberle 2011	5717	26722	2010	26732	40.7%	2.85 [2.71 , 2.98]
Infante 2015	163	1264	22	1186	22.7%	6.95 [4.49 , 10.77]
Subtotal (95% CI)		**29646**		**29576**	**100.0%**	**3.28 [2.40 , 4.48]**
Total events:	6277		2196			
Heterogeneity: Tau² = 0.06; Chi² = 19.61, df = 2 (P < 0.0001); I² = 90%						
Test for overall effect: Z = 7.48 (P < 0.00001)						
2.2.2 at follow-up						
Aberle 2011	10246	26723	3884	26732	56.9%	2.64 [2.55 , 2.73]
Infante 2015	96	1264	17	1186	43.1%	5.30 [3.18 , 8.82]
Subtotal (95% CI)		**27987**		**27918**	**100.0%**	**3.56 [1.81 , 7.01]**
Total events:	10342		3901			
Heterogeneity: Tau² = 0.21; Chi² = 7.17, df = 1 (P = 0.007); I² = 86%						
Test for overall effect: Z = 3.68 (P = 0.0002)						
Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.83), I² = 0%						



Analysis 2.3. Comparison 2: Primary outcome: number of non-invasive and invasive tests - all time points, Outcome 3: Number of invasive test for false positive

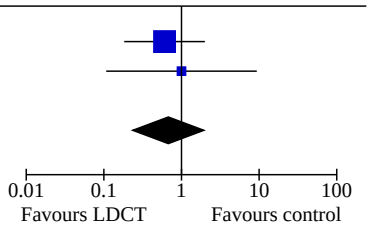
Study or Subgroup	LDCT Events	LDCT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 at baseline						
Gohagan 2005	34	1660	11	1658	7.8%	3.09 [1.57 , 6.07]
Subtotal (95% CI)		**1660**		**1658**	**7.8%**	**3.09 [1.57 , 6.07]**
Total events:	34		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.27 (P = 0.001)						
2.3.2 at follow-up						
Aberle 2011	457	26723	115	26733	86.4%	3.98 [3.24 , 4.87]
Infante 2015	24	1264	7	1186	5.1%	3.22 [1.39 , 7.44]
Pastorino 2012	3	2376	1	1723	0.7%	2.18 [0.23 , 20.90]
Subtotal (95% CI)		**30363**		**29642**	**92.2%**	**3.91 [3.21 , 4.76]**
Total events:	484		123			
Heterogeneity: Tau² = 0.00; Chi² = 0.49, df = 2 (P = 0.78); I² = 0%						
Test for overall effect: Z = 13.55 (P < 0.00001)						
Total (95% CI)		**32023**		**31300**	**100.0%**	**3.84 [3.18 , 4.64]**
Total events:	518		134			
Heterogeneity: Tau² = 0.00; Chi² = 0.92, df = 3 (P = 0.82); I² = 0%						
Test for overall effect: Z = 13.92 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.43, df = 1 (P = 0.51), I² = 0%						



Analysis 2.4. Comparison 2: Primary outcome: number of non-invasive and invasive tests - all time points, Outcome 4: Death postsurgery

Study or Subgroup	LDCT Events	LDCT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Aberle 2011	7	191	4	66	77.7%	0.60 [0.18 , 2.00]
Infante 2015	3	114	1	38	22.3%	1.00 [0.11 , 9.33]
Total (95% CI)		**305**		**104**	**100.0%**	**0.68 [0.24 , 1.94]**
Total events:	10		5			

Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 1 (P = 0.70); I² = 0%
Test for overall effect: Z = 0.73 (P = 0.47)
Test for subgroup differences: Not applicable



Comparison 3. Secondary outcome: all-cause mortality

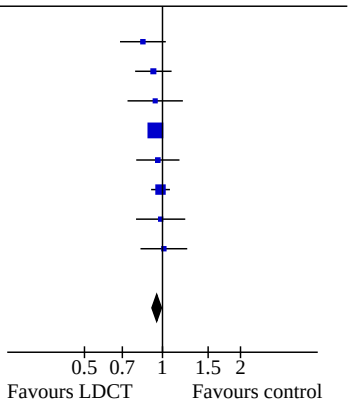
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 All-cause mortality - planned time points (latest time points)	8	91107	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.91, 0.99]
3.2 All-cause mortality - all time points (planned and unplanned)	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.2.1 5 to 6 years	3	11474	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.88, 1.47]
3.2.2 > 6 to 8 years	2	57422	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.89, 0.99]
3.2.3 > 8 to 10 years	6	33685	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.91, 1.03]
3.2.4 > 10 years	2	56658	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.76, 1.09]
3.3 All-cause mortality - planned time points	3		Hazard Ratio (IV, Random, 95% CI)	Subtotals only
3.3.1 any time points	3		Hazard Ratio (IV, Random, 95% CI)	0.98 [0.87, 1.12]
3.4 All-cause mortality by sex - planned time points	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.4.1 females	2	24514	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.76, 1.03]
3.4.2 males	3	49162	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.80, 1.07]
3.5 Cardiovascular mortality - planned and unplanned	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.5.1 8 to 10 years	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.5.2 > 10 years - unplanned	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 3.1. Comparison 3: Secondary outcome: all-cause mortality, Outcome 1: All-cause mortality - planned time points (latest time points)

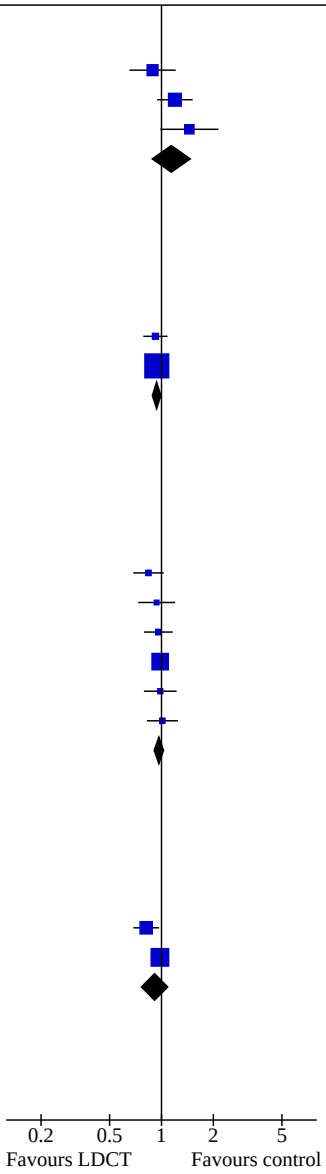
	LDCT		Control			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Paci 2017	154	1613	181	1593	4.3%	0.84 [0.69 , 1.03]	
Field 2021	246	1987	266	1981	6.8%	0.92 [0.78 , 1.08]	
Pastorino 2012	137	2376	106	1723	2.9%	0.94 [0.73 , 1.20]	
Aberle 2011	1877	26722	2000	26732	48.1%	0.94 [0.88 , 1.00]	
Infante 2015	180	1264	176	1186	4.8%	0.96 [0.79 , 1.16]	
De Koning 2020	959	7895	974	7879	25.4%	0.98 [0.90 , 1.07]	
Becker 2020	148	2029	150	2023	3.7%	0.98 [0.79 , 1.22]	
Wille 2016	165	2052	163	2052	4.1%	1.01 [0.82 , 1.25]	
Total (95% CI)		**45938**		**45169**	**100.0%**	**0.95 [0.91 , 0.99]**	
Total events:	3866		4016				

Heterogeneity: Tau² = 0.00; Chi² = 2.78, df = 7 (P = 0.90); I² = 0%
Test for overall effect: Z = 2.41 (P = 0.02)
Test for subgroup differences: Not applicable



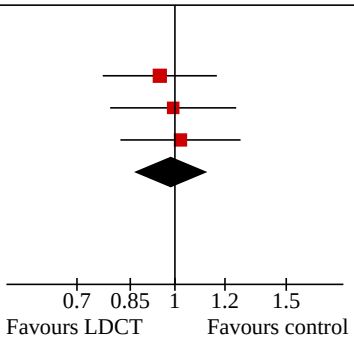
Analysis 3.2. Comparison 3: Secondary outcome: all-cause mortality, Outcome 2: All-cause mortality - all time points (planned and unplanned)

Study or Subgroup	LDCT Events	LDCT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 5 to 6 years						
Becker 2020	73	2029	82	2023	33.0%	0.89 [0.65 , 1.21]
Gohagan 2005	139	1660	116	1658	41.3%	1.20 [0.94 , 1.52]
Wille 2016	61	2052	42	2052	25.8%	1.45 [0.99 , 2.14]
Subtotal (95% CI)		**5741**		**5733**	**100.0%**	**1.14 [0.88 , 1.47]**
Total events:	273		240			
Heterogeneity: Tau² = 0.03; Chi² = 4.17, df = 2 (P = 0.12); I² = 52%						
Test for overall effect: Z = 1.01 (P = 0.31)						
3.2.2 > 6 to 8 years						
Field 2021	246	1987	266	1981	12.3%	0.92 [0.78 , 1.08]
Aberle 2011	1877	26722	2000	26732	87.7%	0.94 [0.88 , 1.00]
Subtotal (95% CI)		**28709**		**28713**	**100.0%**	**0.94 [0.89 , 0.99]**
Total events:	2123		2266			
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.84); I² = 0%						
Test for overall effect: Z = 2.25 (P = 0.02)						
3.2.3 > 8 to 10 years						
Paci 2017	154	1613	181	1593	9.5%	0.84 [0.69 , 1.03]
Pastorino 2012	137	2376	106	1723	6.5%	0.94 [0.73 , 1.20]
Infante 2015	180	1264	176	1186	10.6%	0.96 [0.79 , 1.16]
De Koning 2020	959	7895	974	7879	56.1%	0.98 [0.90 , 1.07]
Becker 2020	148	2029	150	2023	8.2%	0.98 [0.79 , 1.22]
Wille 2016	165	2052	163	2052	9.1%	1.01 [0.82 , 1.25]
Subtotal (95% CI)		**17229**		**16456**	**100.0%**	**0.97 [0.91 , 1.03]**
Total events:	1743		1750			
Heterogeneity: Tau² = 0.00; Chi² = 2.25, df = 5 (P = 0.81); I² = 0%						
Test for overall effect: Z = 1.10 (P = 0.27)						
3.2.4 > 10 years						
Paci 2017	203	1613	246	1593	39.0%	0.81 [0.69 , 0.97]
Aberle 2011	5253	26722	5366	26730	61.0%	0.98 [0.95 , 1.01]
Subtotal (95% CI)		**28335**		**28323**	**100.0%**	**0.91 [0.76 , 1.09]**
Total events:	5456		5612			
Heterogeneity: Tau² = 0.01; Chi² = 4.19, df = 1 (P = 0.04); I² = 76%						
Test for overall effect: Z = 1.03 (P = 0.30)						



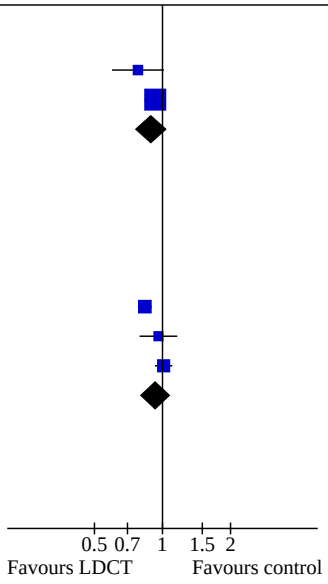
Analysis 3.3. Comparison 3: Secondary outcome: all-cause mortality, Outcome 3: All-cause mortality - planned time points

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
3.3.1 any time points				
Infante 2015	-0.055	0.106	36.7%	0.95 [0.77 , 1.17]
Becker 2020	-0.0063	0.1171	30.1%	0.99 [0.79 , 1.25]
Wille 2016	0.0203	0.1116	33.1%	1.02 [0.82 , 1.27]
Subtotal (95% CI)			**100.0%**	**0.98 [0.87 , 1.12]**
Heterogeneity: Tau² = 0.00; Chi² = 0.25, df = 2 (P = 0.88); I² = 0%				
Test for overall effect: Z = 0.24 (P = 0.81)				
Test for subgroup differences: Not applicable				

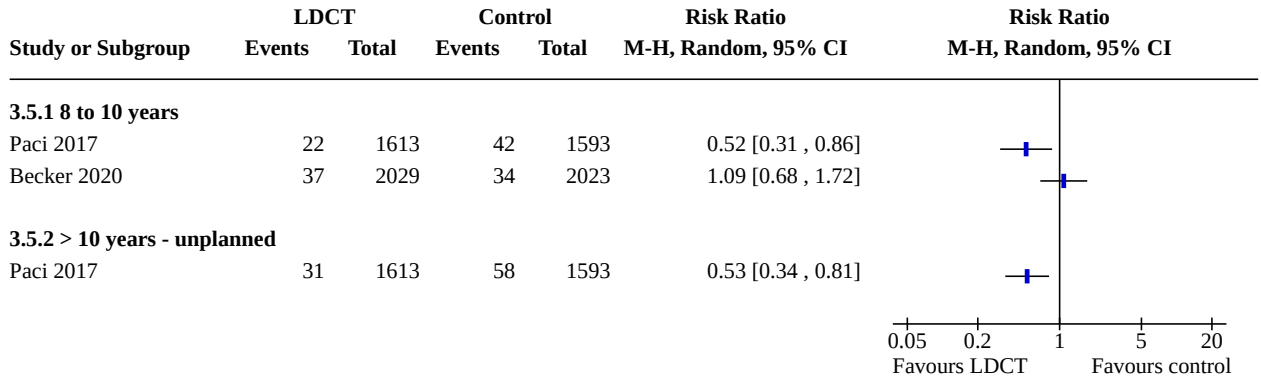


Analysis 3.4. Comparison 3: Secondary outcome: all-cause mortality, Outcome 4: All-cause mortality by sex - planned time points

Study or Subgroup	LDCT Events	LDCT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
3.4.1 females						
De Koning 2020	91	1312	114	1280	25.7%	0.78 [0.60 , 1.01]
Aberle 2011	574	10953	619	10969	74.3%	0.93 [0.83 , 1.04]
Subtotal (95% CI)		**12265**		**12249**	**100.0%**	**0.89 [0.76 , 1.03]**
Total events:	665		733			
Heterogeneity: Tau² = 0.00; Chi² = 1.45, df = 1 (P = 0.23); I² = 31%						
Test for overall effect: Z = 1.55 (P = 0.12)						
3.4.2 males						
Aberle 2011	1338	17769	1420	15761	38.8%	0.84 [0.78 , 0.90]
Infante 2015	180	1264	176	1186	24.3%	0.96 [0.79 , 1.16]
De Koning 2020	868	6583	860	6599	37.0%	1.01 [0.93 , 1.10]
Subtotal (95% CI)		**25616**		**23546**	**100.0%**	**0.93 [0.80 , 1.07]**
Total events:	2386		2456			
Heterogeneity: Tau² = 0.01; Chi² = 11.30, df = 2 (P = 0.004); I² = 82%						
Test for overall effect: Z = 1.03 (P = 0.30)						
Test for subgroup differences: Chi² = 0.17, df = 1 (P = 0.68), I² = 0%						



Analysis 3.5. Comparison 3: Secondary outcome: all-cause mortality, Outcome 5: Cardiovascular mortality - planned and unplanned

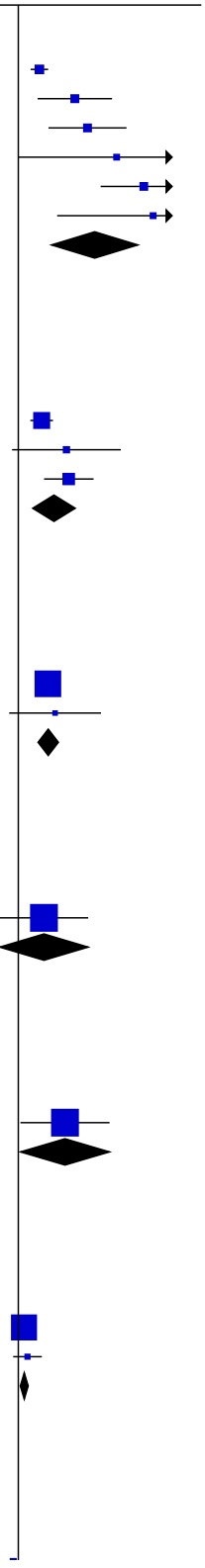


Comparison 4. Secondary outcome: lung cancer incidence

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Lung cancer incidence - by different time points	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1.1 at baseline	6	79900	Risk Ratio (M-H, Random, 95% CI)	4.98 [2.01, 12.35]
4.1.2 at year 1	3	73345	Risk Ratio (M-H, Random, 95% CI)	2.12 [1.35, 3.31]
4.1.3 at year 2	2	57556	Risk Ratio (M-H, Random, 95% CI)	1.88 [1.51, 2.32]
4.1.4 at year 3	1	4104	Risk Ratio (M-H, Random, 95% CI)	1.71 [0.68, 4.35]
4.1.5 at year 4	1	4104	Risk Ratio (M-H, Random, 95% CI)	2.67 [1.05, 6.80]
4.1.6 5 to 7 years	2	57506	Risk Ratio (M-H, Random, 95% CI)	1.13 [1.04, 1.23]
4.1.7 > 7 years	8	88528	Risk Ratio (M-H, Random, 95% CI)	1.17 [1.02, 1.33]
4.2 Lung cancer incidence - by control group at ≥ 10 years	6	82110	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.99, 1.34]
4.2.1 usual care	5	28656	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.99, 1.48]
4.2.2 CXR	1	53454	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.95, 1.08]
4.3 Overdiagnosis at ≥ 10 years	6		Risk Difference (IV, Random, 95% CI)	Subtotals only
4.3.1 usual care	5	28656	Risk Difference (IV, Random, 95% CI)	0.18 [-0.00, 0.36]
4.3.2 CXR	1	53454	Risk Difference (IV, Random, 95% CI)	0.01 [-0.05, 0.07]

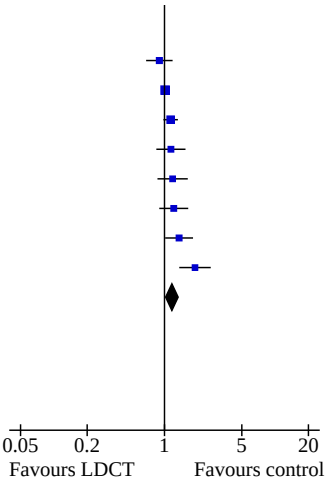
Analysis 4.1. Comparison 4: Secondary outcome: lung cancer incidence, Outcome 1: Lung cancer incidence - by different time points

Study or Subgroup	LDCT Events	LDCT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
4.1.1 at baseline						
Aberle 2011	288	26722	185	26730	22.3%	1.56 [1.30 , 1.87]
Infante 2015	28	1276	8	1196	19.3%	3.28 [1.50 , 7.17]
Gohagan 2005	30	1660	7	1658	19.0%	4.28 [1.89 , 9.72]
Blanchon 2007	8	385	1	380	10.4%	7.90 [0.99 , 62.83]
De Koning 2020	70	7900	5	7889	18.4%	13.98 [5.65 , 34.62]
Wille 2016	17	2052	1	2052	10.7%	17.00 [2.26 , 127.62]
Subtotal (95% CI)		**39995**		**39905**	**100.0%**	**4.98 [2.01 , 12.35]**
Total events:	441		207			
Heterogeneity: Tau² = 0.95; Chi² = 37.15, df = 5 (P < 0.00001); I² = 87%						
Test for overall effect: Z = 3.47 (P = 0.0005)						
4.1.2 at year 1						
Aberle 2011	178	26722	109	26730	53.6%	1.63 [1.29 , 2.07]
Wille 2016	11	2052	4	2052	12.3%	2.75 [0.88 , 8.62]
De Koning 2020	55	7900	19	7889	34.1%	2.89 [1.72 , 4.87]
Subtotal (95% CI)		**36674**		**36671**	**100.0%**	**2.12 [1.35 , 3.31]**
Total events:	244		132			
Heterogeneity: Tau² = 0.08; Chi² = 4.34, df = 2 (P = 0.11); I² = 54%						
Test for overall effect: Z = 3.28 (P = 0.001)						
4.1.3 at year 2						
Aberle 2011	227	26722	122	26730	95.1%	1.86 [1.49 , 2.32]
Wille 2016	13	2052	6	2052	4.9%	2.17 [0.83 , 5.69]
Subtotal (95% CI)		**28774**		**28782**	**100.0%**	**1.88 [1.51 , 2.32]**
Total events:	240		128			
Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.76); I² = 0%						
Test for overall effect: Z = 5.76 (P < 0.00001)						
4.1.4 at year 3						
Wille 2016	12	2052	7	2052	100.0%	1.71 [0.68 , 4.35]
Subtotal (95% CI)		**2052**		**2052**	**100.0%**	**1.71 [0.68 , 4.35]**
Total events:	12		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.14 (P = 0.26)						
4.1.5 at year 4						
Wille 2016	16	2052	6	2052	100.0%	2.67 [1.05 , 6.80]
Subtotal (95% CI)		**2052**		**2052**	**100.0%**	**2.67 [1.05 , 6.80]**
Total events:	16		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.05 (P = 0.04)						
4.1.6 5 to 7 years						
Aberle 2011	1060	26722	941	26732	92.4%	1.13 [1.03 , 1.23]
Becker 2020	90	2029	74	2023	7.6%	1.21 [0.90 , 1.64]
Subtotal (95% CI)		**28751**		**28755**	**100.0%**	**1.13 [1.04 , 1.23]**
Total events:	1150		1015			
Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 1 (P = 0.65); I² = 0%						
Test for overall effect: Z = 2.96 (P = 0.003)						
4.1.7 > 7 years						
Paci 2017	91	1613	100	1593	11.2%	0.90 [0.68 , 1.18]



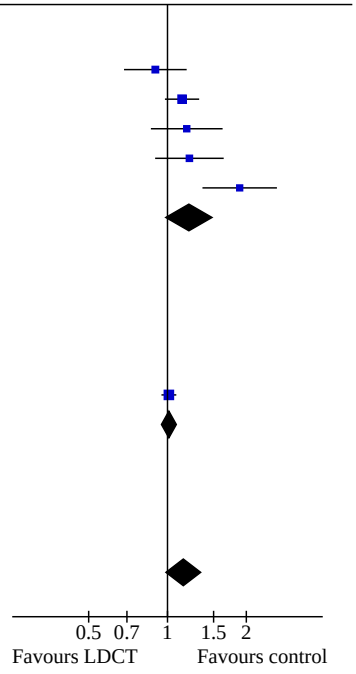
Analysis 4.1. (Continued)

4.1.7 > 7 years						
Paci 2017	91	1613	100	1593	11.2%	0.90 [0.68 , 1.18]
Aberle 2011	1701	26722	1681	26732	21.4%	1.01 [0.95 , 1.08]
De Koning 2020	344	6583	304	6612	17.4%	1.14 [0.98 , 1.32]
Field 2021	86	1987	75	1981	10.1%	1.14 [0.84 , 1.55]
Pastorino 2012	98	2376	60	1723	9.7%	1.18 [0.86 , 1.62]
Becker 2020	90	2029	74	2023	10.2%	1.21 [0.90 , 1.64]
Infante 2015	104	1264	72	1186	10.6%	1.36 [1.01 , 1.81]
Wille 2016	100	2052	53	2052	9.3%	1.89 [1.36 , 2.62]
Subtotal (95% CI)		**44626**		**43902**	**100.0%**	**1.17 [1.02 , 1.33]**
Total events:	2614		2419			
Heterogeneity: Tau² = 0.02; Chi² = 20.25, df = 7 (P = 0.005); I² = 65%						
Test for overall effect: Z = 2.32 (P = 0.02)						



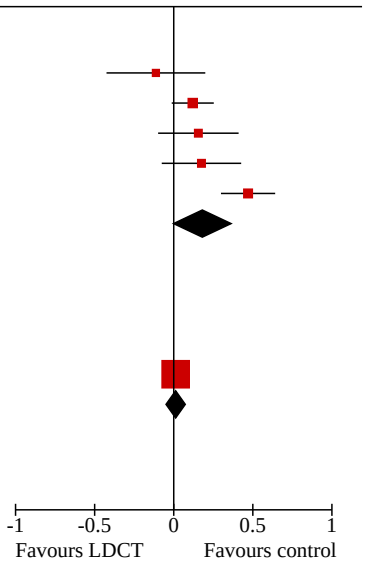
Analysis 4.2. Comparison 4: Secondary outcome: lung cancer incidence, Outcome 2: Lung cancer incidence - by control group at ≥ 10 years

	LDCT		Control			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
4.2.1 usual care							
Paci 2017	91	1613	100	1593	14.4%	0.90 [0.68 , 1.18]	
De Koning 2020	344	6583	304	6612	21.6%	1.14 [0.98 , 1.32]	
Pastorino 2012	98	2376	60	1723	12.6%	1.18 [0.86 , 1.62]	
Becker 2020	90	2029	74	2023	13.2%	1.21 [0.90 , 1.64]	
Wille 2016	100	2052	53	2052	12.1%	1.89 [1.36 , 2.62]	
Subtotal (95% CI)		**14653**		**14003**	**74.0%**	**1.21 [0.99 , 1.48]**	
Total events:	723		591				
Heterogeneity: Tau² = 0.03; Chi² = 11.92, df = 4 (P = 0.02); I² = 66%							
Test for overall effect: Z = 1.82 (P = 0.07)							
4.2.2 CXR							
Aberle 2011	1701	26722	1681	26732	26.0%	1.01 [0.95 , 1.08]	
Subtotal (95% CI)		**26722**		**26732**	**26.0%**	**1.01 [0.95 , 1.08]**	
Total events:	1701		1681				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.37 (P = 0.71)							
Total (95% CI)		**41375**		**40735**	**100.0%**	**1.15 [0.99 , 1.34]**	
Total events:	2424		2272				
Heterogeneity: Tau² = 0.02; Chi² = 17.24, df = 5 (P = 0.004); I² = 71%							
Test for overall effect: Z = 1.79 (P = 0.07)							
Test for subgroup differences: Chi² = 2.62, df = 1 (P = 0.11), I² = 61.8%							



Analysis 4.3. Comparison 4: Secondary outcome: lung cancer incidence, Outcome 3: Overdiagnosis at ≥ 10 years

Study or Subgroup	RD	SE	LDCT Total	Control Total	Weight	Risk Difference IV, Random, 95% CI
4.3.1 usual care						
Paci 2017	-0.1127	0.1593	1613	1593	15.5%	-0.11 [-0.42 , 0.20]
De Koning 2020	0.1202	0.0678	6583	6612	24.8%	0.12 [-0.01 , 0.25]
Pastorino 2012	0.1557	0.1298	2376	1723	18.3%	0.16 [-0.10 , 0.41]
Becker 2020	0.1753	0.1281	2029	2023	18.5%	0.18 [-0.08 , 0.43]
Wille 2016	0.47	0.0874	2052	2052	22.8%	0.47 [0.30 , 0.64]
Subtotal (95% CI)			**14653**	**14003**	**100.0%**	**0.18 [-0.00 , 0.36]**
Heterogeneity: Tau² = 0.03; Chi² = 14.93, df = 4 (P = 0.005); I² = 73%						
Test for overall effect: Z = 1.95 (P = 0.05)						
4.3.2 CXR						
Aberle 2011	0.0121	0.031	26722	26732	100.0%	0.01 [-0.05 , 0.07]
Subtotal (95% CI)			**26722**	**26732**	**100.0%**	**0.01 [-0.05 , 0.07]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.39 (P = 0.70)						
Test for subgroup differences: Chi² = 2.97, df = 1 (P = 0.08), I² = 66.3%						



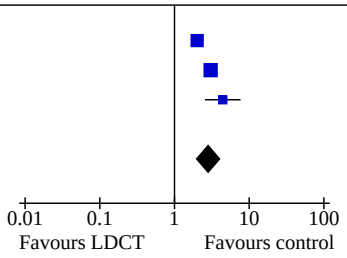
Comparison 5. Secondary outcome: false positives, negatives and recalls (number of screens)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 False positive at baseline	3	56101	Risk Ratio (M-H, Random, 95% CI)	2.82 [1.98, 4.01]
5.2 False negative	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.2.1 baseline	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.2.2 at year 1	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.2.3 at year 2	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.3 Recall rates at baseline	2	55480	Risk Ratio (M-H, Random, 95% CI)	5.31 [1.73, 16.34]

Analysis 5.1. Comparison 5: Secondary outcome: false positives, negatives and recalls (number of screens), Outcome 1: False positive at baseline

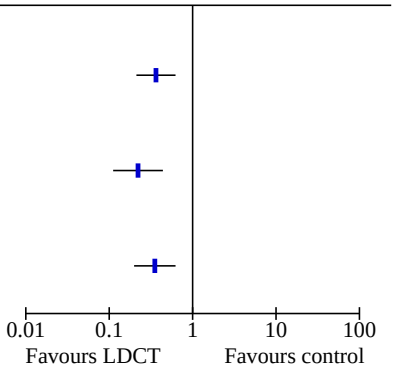
Study or Subgroup	LDCT Events	LDCT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Gohagan 2005	286	1586	139	1550	37.4%	2.01 [1.66 , 2.43]
Aberle 2011	6911	26309	2243	26035	41.7%	3.05 [2.92 , 3.19]
Blanchon 2007	73	336	14	285	20.8%	4.42 [2.55 , 7.66]
Total (95% CI)		**28231**		**27870**	**100.0%**	**2.82 [1.98 , 4.01]**
Total events:	7270		2396			

Heterogeneity: Tau² = 0.08; Chi² = 19.42, df = 2 (P < 0.0001); I² = 90%
Test for overall effect: Z = 5.75 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 5.2. Comparison 5: Secondary outcome: false positives, negatives and recalls (number of screens), Outcome 2: False negative

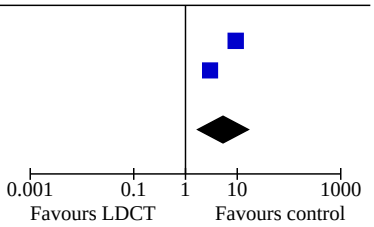
Study or Subgroup	LDCT Events	LDCT Total	Control Events	Control Total	Risk Ratio M-H, Random, 95% CI
5.2.1 baseline					
Aberle 2011	18	26309	49	26035	0.36 [0.21 , 0.62]
5.2.2 at year 1					
Aberle 2011	10	24715	44	24089	0.22 [0.11 , 0.44]
5.2.3 at year 2					
Aberle 2011	16	24102	44	23346	0.35 [0.20 , 0.62]



Analysis 5.3. Comparison 5: Secondary outcome: false positives, negatives and recalls (number of screens), Outcome 3: Recall rates at baseline

Study or Subgroup	LDCT Events	LDCT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Aberle 2011	5153	26309	546	26035	50.5%	9.34 [8.57 , 10.18]
Gohagan 2005	232	1586	76	1550	49.5%	2.98 [2.32 , 3.83]
Total (95% CI)		**27895**		**27585**	**100.0%**	**5.31 [1.73 , 16.34]**
Total events:	5385		622			

Heterogeneity: Tau² = 0.65; Chi² = 72.50, df = 1 (P < 0.00001); I² = 99%
Test for overall effect: Z = 2.91 (P = 0.004)
Test for subgroup differences: Not applicable

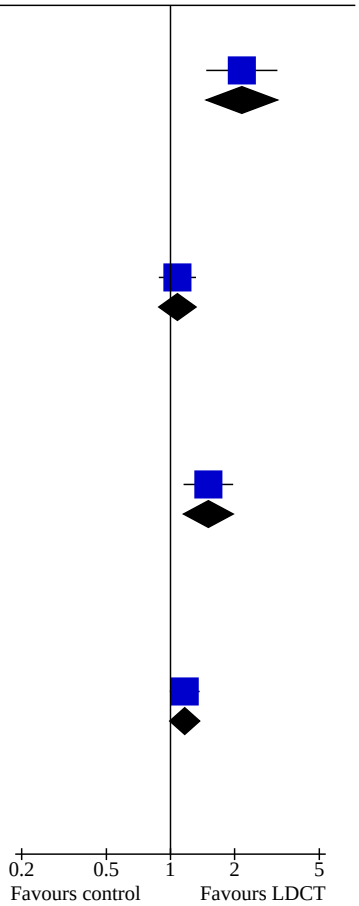


Comparison 6. Secondary outcome: impact on smoking behaviour

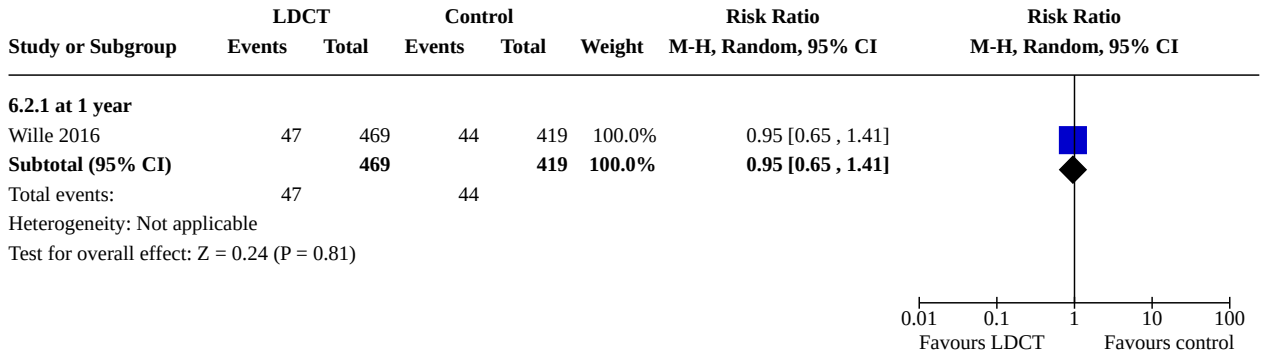
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 stop smoking	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1.1 at 2 weeks	1	1545	Risk Ratio (M-H, Random, 95% CI)	2.16 [1.47, 3.18]
6.1.2 at 1 year	1	3124	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.88, 1.32]
6.1.3 within 2 years	1	1524	Risk Ratio (M-H, Random, 95% CI)	1.51 [1.15, 1.97]
6.1.4 at year 4	1	2447	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.99, 1.37]
6.2 smoking relapse	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.2.1 at 1 year	1	888	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.65, 1.41]

Analysis 6.1. Comparison 6: Secondary outcome: impact on smoking behaviour, Outcome 1: stop smoking

Study or Subgroup	LDCT Events	LDCT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
6.1.1 at 2 weeks						
Field 2021	75	758	36	787	100.0%	2.16 [1.47 , 3.18]
Subtotal (95% CI)		**758**		**787**	**100.0%**	**2.16 [1.47 , 3.18]**
Total events:	75		36			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.93 (P < 0.0001)						
6.1.2 at 1 year						
Wille 2016	174	1545	165	1579	100.0%	1.08 [0.88 , 1.32]
Subtotal (95% CI)		**1545**		**1579**	**100.0%**	**1.08 [0.88 , 1.32]**
Total events:	174		165			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.47)						
6.1.3 within 2 years						
Field 2021	115	749	79	775	100.0%	1.51 [1.15 , 1.97]
Subtotal (95% CI)		**749**		**775**	**100.0%**	**1.51 [1.15 , 1.97]**
Total events:	115		79			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.99 (P = 0.003)						
6.1.4 at year 4						
Paci 2017	249	1186	227	1261	100.0%	1.17 [0.99 , 1.37]
Subtotal (95% CI)		**1186**		**1261**	**100.0%**	**1.17 [0.99 , 1.37]**
Total events:	249		227			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.87 (P = 0.06)						



Analysis 6.2. Comparison 6: Secondary outcome: impact on smoking behaviour, Outcome 2: smoking relapse



Comparison 7. Secondary outcome: health-related quality of life

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Anxiety - at 10 months to 5 years (change over time and end-points)	3	8153	Std. Mean Difference (IV, Random, 95% CI)	-0.43 [-0.59, -0.27]
7.2 Quality of life measures at different time points	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.2.1 Physical component summary of short-form 12 (PCS) at baseline	1	1288	Mean Difference (IV, Random, 95% CI)	-0.17 [-1.21, 0.87]
7.2.2 Physical component summary of short-form 12 (PCS) at 2 years	1	931	Mean Difference (IV, Random, 95% CI)	0.88 [-0.34, 2.10]
7.2.3 Mental component summary of short-form 12 (MCS) at baseline	1	1288	Mean Difference (IV, Random, 95% CI)	-0.06 [-1.42, 1.30]
7.2.4 Mental component summary of short-form 12 (MCS) at 2 years	1	931	Mean Difference (IV, Random, 95% CI)	0.81 [-0.65, 2.27]
7.2.5 EuroQol questionnaire visual analogue scale (EQ-5D VAS) (1-100) at baseline	1	1288	Mean Difference (IV, Random, 95% CI)	0.69 [-0.98, 2.36]
7.2.6 EuroQol questionnaire visual analogue scale (EQ-5D VAS) (1-100) at 2 years	1	1010	Mean Difference (IV, Random, 95% CI)	2.08 [0.18, 3.98]
7.2.7 Spielberger State-Trait Anxiety Inventory (STAI-6) at baseline	1	1288	Mean Difference (IV, Random, 95% CI)	-0.48 [-1.63, 0.67]
7.2.8 Spielberger State-Trait Anxiety Inventory (STAI-6) at 2 years	1	931	Mean Difference (IV, Random, 95% CI)	-0.75 [-1.99, 0.49]
7.2.9 Impact of event scale (IES) total at baseline	1	1288	Mean Difference (IV, Random, 95% CI)	0.03 [-0.88, 0.94]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.2.10 Anxiety - at baseline	1	4037	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.11, -0.03]
7.2.11 Impact of event scale (IES) total at 2 years	1	931	Mean Difference (IV, Random, 95% CI)	-0.31 [-1.30, 0.68]
7.2.12 Anxiety - at 10-27 months	1	4037	Mean Difference (IV, Random, 95% CI)	-0.36 [-0.57, -0.15]
7.2.13 Anxiety (0-18) at round 1 to 2	1	3352	Mean Difference (IV, Random, 95% CI)	-0.13 [-0.33, 0.07]
7.2.14 Anxiety (0-18) at round 1 to 5	1	3185	Mean Difference (IV, Random, 95% CI)	-0.51 [-0.76, -0.26]
7.2.15 Depression - at baseline	1	4037	Mean Difference (IV, Random, 95% CI)	-0.06 [-0.10, -0.02]
7.2.16 Depression - at 10-27 months	1	4037	Mean Difference (IV, Random, 95% CI)	-0.24 [-0.40, -0.08]
7.2.17 Behaviour (0-21) at round 1 to 2	1	3337	Mean Difference (IV, Random, 95% CI)	-0.21 [-0.42, 0.00]
7.2.18 Behaviour (0-21) at round 1 to 5	1	3180	Mean Difference (IV, Random, 95% CI)	-0.60 [-0.88, -0.32]
7.2.19 Dejection (0-18) at round 1 to 2	1	3377	Mean Difference (IV, Random, 95% CI)	-0.15 [-0.36, 0.06]
7.2.20 Dejection (0-18) at round 1 to 5	1	3195	Mean Difference (IV, Random, 95% CI)	-0.58 [-0.82, -0.34]
7.2.21 Negative impact on sleep (0-12) round 1 to 2	1	3389	Mean Difference (IV, Random, 95% CI)	-0.14 [-0.32, 0.04]
7.2.22 Negative impact on sleep (0-12) round 1 to 5	1	3198	Mean Difference (IV, Random, 95% CI)	-0.70 [-0.95, -0.45]
7.3 SF-36v2: PCS by different components at baseline and at 6 months	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.3.1 Negative at baseline	1	1381	Mean Difference (IV, Random, 95% CI)	-1.07 [-2.09, -0.05]
7.3.2 Negative at 6 months	1	1019	Mean Difference (IV, Random, 95% CI)	-0.11 [-1.38, 1.16]
7.3.3 SIFs at baseline	1	344	Mean Difference (IV, Random, 95% CI)	0.16 [-2.45, 2.77]
7.3.4 SIFs at 6 months	1	226	Mean Difference (IV, Random, 95% CI)	-1.25 [-4.26, 1.76]

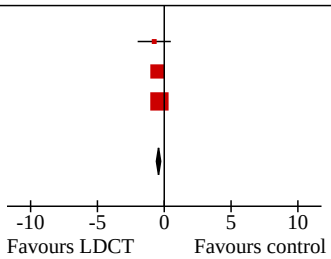
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.3.5 False positive at baseline	1	1024	Mean Difference (IV, Random, 95% CI)	-0.72 [-1.98, 0.54]
7.3.6 False positive at 6 months	1	703	Mean Difference (IV, Random, 95% CI)	-0.78 [-2.42, 0.86]
7.3.7 True positive at baseline	1	63	Mean Difference (IV, Random, 95% CI)	-1.94 [-7.33, 3.45]
7.3.8 True positive at 6 months	1	42	Mean Difference (IV, Random, 95% CI)	-0.20 [-7.32, 6.92]
7.4 SF-36v2: MCS by different components at baseline and 6 months	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.4.1 Negative at baseline	1	1381	Mean Difference (IV, Random, 95% CI)	-0.85 [-1.97, 0.27]
7.4.2 Negative at 6 months	1	1019	Mean Difference (IV, Random, 95% CI)	-0.15 [-1.52, 1.22]
7.4.3 SIFs at baseline	1	344	Mean Difference (IV, Random, 95% CI)	0.63 [-1.94, 3.20]
7.4.4 SIFs at 6 months	1	226	Mean Difference (IV, Random, 95% CI)	0.73 [-2.27, 3.73]
7.4.5 False positive at baseline	1	1024	Mean Difference (IV, Random, 95% CI)	-0.19 [-1.43, 1.05]
7.4.6 False positive at 6 months	1	703	Mean Difference (IV, Random, 95% CI)	-1.02 [-2.67, 0.63]
7.4.7 True positive at baseline	1	63	Mean Difference (IV, Random, 95% CI)	-1.74 [-6.66, 3.18]
7.4.8 True positive at 6 months	1	42	Mean Difference (IV, Random, 95% CI)	0.08 [-8.19, 8.35]
7.5 Anxiety by different results at 1 and 6 months	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.5.1 Negative at 1 month	1	1162	Mean Difference (IV, Random, 95% CI)	-0.26 [-1.79, 1.27]
7.5.2 Negative at 6 months	1	1019	Mean Difference (IV, Random, 95% CI)	-0.33 [-1.91, 1.25]
7.5.3 SIFs at 1 month	1	272	Mean Difference (IV, Random, 95% CI)	-0.06 [-3.52, 3.40]
7.5.4 SIFs at 6 months	1	226	Mean Difference (IV, Random, 95% CI)	-0.60 [-4.26, 3.06]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.5.5 False positive at 1 month	1	835	Mean Difference (IV, Random, 95% CI)	1.77 [-0.04, 3.58]
7.5.6 False positive at 6 months	1	703	Mean Difference (IV, Random, 95% CI)	1.31 [-0.61, 3.23]
7.5.7 True positive at 1 month	1	48	Mean Difference (IV, Random, 95% CI)	1.63 [-6.31, 9.57]
7.5.8 True positive at 6 months	1	42	Mean Difference (IV, Random, 95% CI)	-2.69 [-11.69, 6.31]

Analysis 7.1. Comparison 7: Secondary outcome: health-related quality of life, Outcome 1: Anxiety - at 10 months to 5 years (change over time and endpoints)

Study or Subgroup	SMD	SE	LDCT Total	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
De Koning 2020	-0.75	0.6327	609	322	1.7%	-0.75 [-1.99 , 0.49]
Wille 2016	-0.51	0.1276	1825	1360	40.6%	-0.51 [-0.76 , -0.26]
Field 2021	-0.36	0.1071	2018	2019	57.7%	-0.36 [-0.57 , -0.15]
Total (95% CI)			**4452**	**3701**	**100.0%**	**-0.43 [-0.59 , -0.27]**

Heterogeneity: Tau² = 0.00; Chi² = 1.08, df = 2 (P = 0.58); I² = 0%
Test for overall effect: Z = 5.25 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 7.2. Comparison 7: Secondary outcome: health-related quality of life, Outcome 2: Quality of life measures at different time points

Study or Subgroup	LDCT Mean	LDCT SD	LDCT Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
7.2.1 Physical component summary of short-form 12 (PCS) at baseline								
De Koning 2020	49.5	9.7186	658	49.67	9.386	630	100.0%	-0.17 [-1.21 , 0.87]
Subtotal (95% CI)			**658**			**630**	**100.0%**	**-0.17 [-1.21 , 0.87]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.32 (P = 0.75)								
7.2.2 Physical component summary of short-form 12 (PCS) at 2 years								
De Koning 2020	49.95	9.4245	609	49.07	8.8473	322	100.0%	0.88 [-0.34 , 2.10]
Subtotal (95% CI)			**609**			**322**	**100.0%**	**0.88 [-0.34 , 2.10]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.41 (P = 0.16)								
7.2.3 Mental component summary of short-form 12 (MCS) at baseline								
De Koning 2020	51.66	11.6266	658	51.72	13.1651	630	100.0%	-0.06 [-1.42 , 1.30]
Subtotal (95% CI)			**658**			**630**	**100.0%**	**-0.06 [-1.42 , 1.30]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.09 (P = 0.93)								
7.2.4 Mental component summary of short-form 12 (MCS) at 2 years								
De Koning 2020	52.5	11.3094	609	51.69	10.4891	322	100.0%	0.81 [-0.65 , 2.27]
Subtotal (95% CI)			**609**			**322**	**100.0%**	**0.81 [-0.65 , 2.27]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.09 (P = 0.28)								
7.2.5 EuroQol questionnaire visual analogue scale (EQ-5D VAS) (1-100) at baseline								
De Koning 2020	79.19	12.933	658	78.5	17.2552	630	100.0%	0.69 [-0.98 , 2.36]
Subtotal (95% CI)			**658**			**630**	**100.0%**	**0.69 [-0.98 , 2.36]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.81 (P = 0.42)								
7.2.6 EuroQol questionnaire visual analogue scale (EQ-5D VAS) (1-100) at 2 years								
De Koning 2020	79.53	15.7868	690	77.45	13.6385	320	100.0%	2.08 [0.18 , 3.98]
Subtotal (95% CI)			**690**			**320**	**100.0%**	**2.08 [0.18 , 3.98]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.14 (P = 0.03)								
7.2.7 Spielberger State-Trait Anxiety Inventory (STAI-6) at baseline								
De Koning 2020	33.27	9.9284	658	33.75	11.12	630	100.0%	-0.48 [-1.63 , 0.67]
Subtotal (95% CI)			**658**			**630**	**100.0%**	**-0.48 [-1.63 , 0.67]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.82 (P = 0.41)								
7.2.8 Spielberger State-Trait Anxiety Inventory (STAI-6) at 2 years								
De Koning 2020	32.67	9.5501	609	33.42	8.9385	322	100.0%	-0.75 [-1.99 , 0.49]
Subtotal (95% CI)			**609**			**322**	**100.0%**	**-0.75 [-1.99 , 0.49]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.19 (P = 0.23)								
7.2.9 Impact of event scale (IES) total at baseline								
De Koning 2020	4.05	7.8382	658	4.02	8.8193	630	100.0%	0.03 [-0.88 , 0.94]
Subtotal (95% CI)			**658**			**630**	**100.0%**	**0.03 [-0.88 , 0.94]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.06 (P = 0.95)								
7.2.10 Anxiety - at baseline								
Field 2021	1.54	0.6872	2018	1.61	0.6874	2019	100.0%	-0.07 [-0.11 , -0.03]
Subtotal (95% CI)			**2018**			**2019**	**100.0%**	**-0.07 [-0.11 , -0.03]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.24 (P = 0.001)								

Analysis 7.2. (Continued)

Heterogeneity: Not applicable
Test for overall effect: Z = 3.24 (P = 0.001)

7.2.11 Impact of event scale (IES) total at 2 years

De Koning 2020	3.72	7.5396	609	4.03	7.2055	322	100.0%	-0.31 [-1.30 , 0.68]
Subtotal (95% CI)			**609**			**322**	**100.0%**	**-0.31 [-1.30 , 0.68]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.61 (P = 0.54)

7.2.12 Anxiety - at 10-27 months

Field 2021	3.66	3.2069	2018	4.02	3.6659	2019	100.0%	-0.36 [-0.57 , -0.15]
Subtotal (95% CI)			**2018**			**2019**	**100.0%**	**-0.36 [-0.57 , -0.15]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.32 (P = 0.0009)

7.2.13 Anxiety (0-18) at round 1 to 2

Wille 2016	0.05	2.8992	1913	0.18	2.9007	1439	100.0%	-0.13 [-0.33 , 0.07]
Subtotal (95% CI)			**1913**			**1439**	**100.0%**	**-0.13 [-0.33 , 0.07]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.28 (P = 0.20)

7.2.14 Anxiety (0-18) at round 1 to 5

Wille 2016	-0.26	2.8316	1825	0.25	3.9478	1360	100.0%	-0.51 [-0.76 , -0.26]
Subtotal (95% CI)			**1825**			**1360**	**100.0%**	**-0.51 [-0.76 , -0.26]**

Heterogeneity: Not applicable
Test for overall effect: Z = 4.05 (P < 0.0001)

7.2.15 Depression - at baseline

Field 2021	1.33	0.6872	2018	1.39	0.6874	2019	100.0%	-0.06 [-0.10 , -0.02]
Subtotal (95% CI)			**2018**			**2019**	**100.0%**	**-0.06 [-0.10 , -0.02]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.77 (P = 0.006)

7.2.16 Depression - at 10-27 months

Field 2021	2.77	2.2906	2018	3.01	2.7494	2019	100.0%	-0.24 [-0.40 , -0.08]
Subtotal (95% CI)			**2018**			**2019**	**100.0%**	**-0.24 [-0.40 , -0.08]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.01 (P = 0.003)

7.2.17 Behaviour (0-21) at round 1 to 2

Wille 2016	1.06	2.8962	1909	1.27	3.2749	1428	100.0%	-0.21 [-0.42 , 0.00]
Subtotal (95% CI)			**1909**			**1428**	**100.0%**	**-0.21 [-0.42 , 0.00]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.92 (P = 0.05)

7.2.18 Behaviour (0-21) at round 1 to 5

Wille 2016	0.77	3.0503	1826	1.37	4.5018	1354	100.0%	-0.60 [-0.88 , -0.32]
Subtotal (95% CI)			**1826**			**1354**	**100.0%**	**-0.60 [-0.88 , -0.32]**

Heterogeneity: Not applicable
Test for overall effect: Z = 4.24 (P < 0.0001)

7.2.19 Dejection (0-18) at round 1 to 2

Wille 2016	0.43	2.9075	1924	0.58	3.1092	1453	100.0%	-0.15 [-0.36 , 0.06]
Subtotal (95% CI)			**1924**			**1453**	**100.0%**	**-0.15 [-0.36 , 0.06]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.43 (P = 0.15)

7.2.20 Dejection (0-18) at round 1 to 5

Wille 2016	0.09	1.0918	1834	0.67	4.3254	1361	100.0%	-0.58 [-0.82 , -0.34]
Subtotal (95% CI)			**1834**			**1361**	**100.0%**	**-0.58 [-0.82 , -0.34]**

Heterogeneity: Not applicable
Test for overall effect: Z = 4.83 (P < 0.00001)

Analysis 7.2. (Continued)

Test for overall effect: Z = 4.83 (P < 0.00001)

7.2.21 Negative impact on sleep (0-12) round 1 to 2

Wille 2016	1.01	2.466	1933	1.15	2.7233	1456	100.0%	-0.14 [-0.32 , 0.04]
Subtotal (95% CI)			**1933**			**1456**	**100.0%**	**-0.14 [-0.32 , 0.04]**

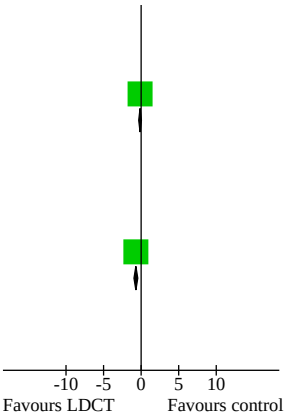
Heterogeneity: Not applicable
Test for overall effect: Z = 1.54 (P = 0.12)

7.2.22 Negative impact on sleep (0-12) round 1 to 5

Wille 2016	0.83	2.616	1828	1.53	4.151	1370	100.0%	-0.70 [-0.95 , -0.45]
Subtotal (95% CI)			**1828**			**1370**	**100.0%**	**-0.70 [-0.95 , -0.45]**

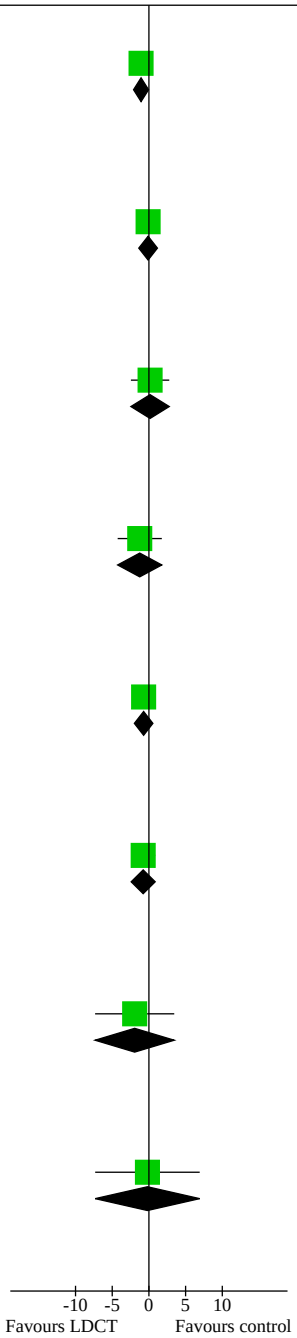
Heterogeneity: Not applicable
Test for overall effect: Z = 5.48 (P < 0.00001)

Test for subgroup differences: Chi² = 88.25, df = 21 (P < 0.00001), I² = 76.2%



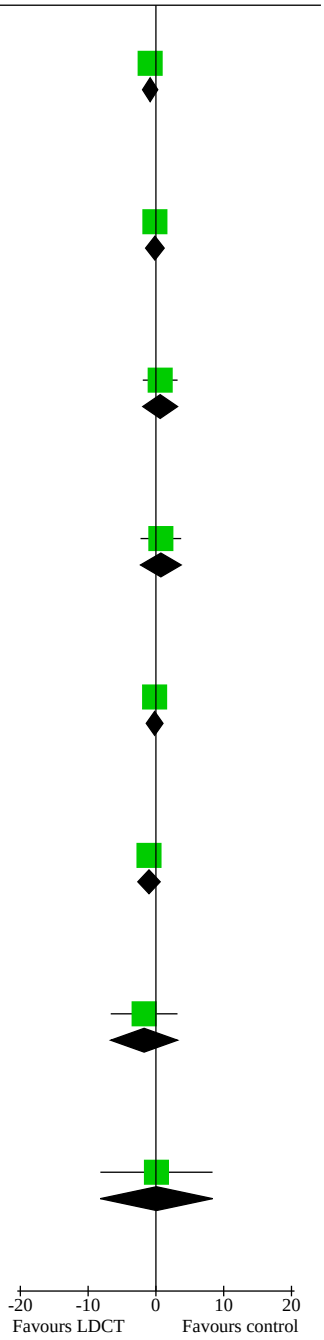
Analysis 7.3. Comparison 7: Secondary outcome: health-related quality of life, Outcome 3: SF-36v2: PCS by different components at baseline and at 6 months

Study or Subgroup	LDCT Mean	LDCT SD	LDCT Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
7.3.1 Negative at baseline								
Aberle 2011	48.16	8.97	949	49.23	8.99	432	100.0%	-1.07 [-2.09 , -0.05]
Subtotal (95% CI)			**949**			**432**	**100.0%**	**-1.07 [-2.09 , -0.05]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.05 (P = 0.04)								
7.3.2 Negative at 6 months								
Aberle 2011	47.89	9.17	691	48	9.89	328	100.0%	-0.11 [-1.38 , 1.16]
Subtotal (95% CI)			**691**			**328**	**100.0%**	**-0.11 [-1.38 , 1.16]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.17 (P = 0.87)								
7.3.3 SIFs at baseline								
Aberle 2011	48.38	9.31	268	48.22	10.51	76	100.0%	0.16 [-2.45 , 2.77]
Subtotal (95% CI)			**268**			**76**	**100.0%**	**0.16 [-2.45 , 2.77]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.12 (P = 0.90)								
7.3.4 SIFs at 6 months								
Aberle 2011	47.2	9.35	177	48.45	9.55	49	100.0%	-1.25 [-4.26 , 1.76]
Subtotal (95% CI)			**177**			**49**	**100.0%**	**-1.25 [-4.26 , 1.76]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.81 (P = 0.42)								
7.3.5 False positive at baseline								
Aberle 2011	47.92	9.98	689	48.64	9.5	335	100.0%	-0.72 [-1.98 , 0.54]
Subtotal (95% CI)			**689**			**335**	**100.0%**	**-0.72 [-1.98 , 0.54]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.12 (P = 0.26)								
7.3.6 False positive at 6 months								
Aberle 2011	47.08	10.16	489	47.86	10.19	214	100.0%	-0.78 [-2.42 , 0.86]
Subtotal (95% CI)			**489**			**214**	**100.0%**	**-0.78 [-2.42 , 0.86]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.93 (P = 0.35)								
7.3.7 True positive at baseline								
Aberle 2011	46.58	11.33	41	48.52	9.88	22	100.0%	-1.94 [-7.33 , 3.45]
Subtotal (95% CI)			**41**			**22**	**100.0%**	**-1.94 [-7.33 , 3.45]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.71 (P = 0.48)								
7.3.8 True positive at 6 months								
Aberle 2011	38.28	12.57	29	38.48	10.04	13	100.0%	-0.20 [-7.32 , 6.92]
Subtotal (95% CI)			**29**			**13**	**100.0%**	**-0.20 [-7.32 , 6.92]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.06 (P = 0.96)								
Test for subgroup differences: $Chi^2 = 2.11$, df = 7 (P = 0.95), $I^2 = 0\%$								

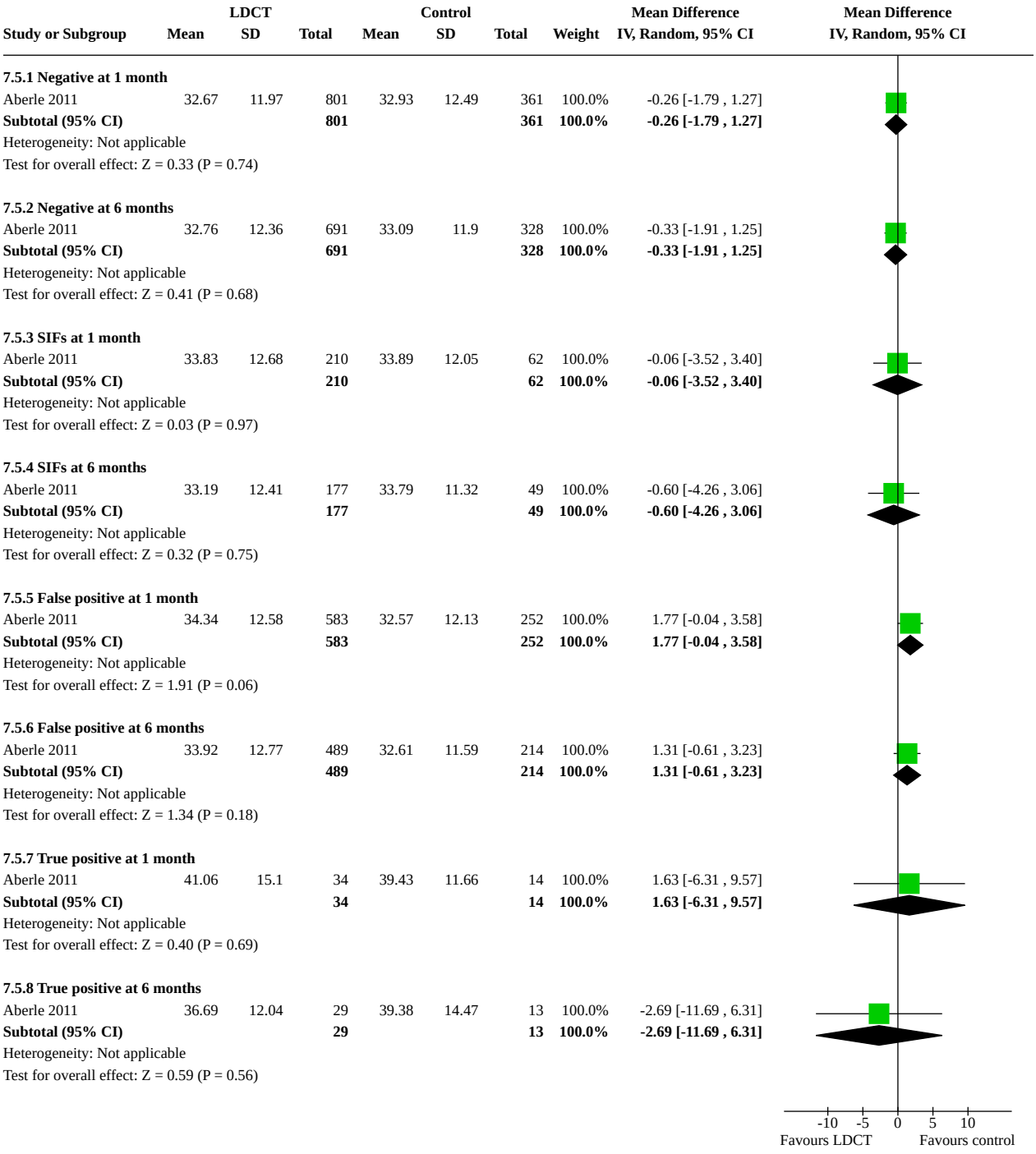


Analysis 7.4. Comparison 7: Secondary outcome: health-related quality of life, Outcome 4: SF-36v2: MCS by different components at baseline and 6 months

Study or Subgroup	LDCT Mean	LDCT SD	LDCT Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
7.4.1 Negative at baseline								
Aberle 2011	51.89	10.19	949	52.74	9.72	432	100.0%	-0.85 [-1.97 , 0.27]
Subtotal (95% CI)			**949**			**432**	**100.0%**	**-0.85 [-1.97 , 0.27]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.48 (P = 0.14)								
7.4.2 Negative at 6 months								
Aberle 2011	51.36	10.55	691	51.51	10.39	328	100.0%	-0.15 [-1.52 , 1.22]
Subtotal (95% CI)			**691**			**328**	**100.0%**	**-0.15 [-1.52 , 1.22]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.21 (P = 0.83)								
7.4.3 SIFs at baseline								
Aberle 2011	51.52	9.83	268	50.89	10.14	76	100.0%	0.63 [-1.94 , 3.20]
Subtotal (95% CI)			**268**			**76**	**100.0%**	**0.63 [-1.94 , 3.20]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.48 (P = 0.63)								
7.4.4 SIFs at 6 months								
Aberle 2011	51.77	10.49	177	51.04	9.18	49	100.0%	0.73 [-2.27 , 3.73]
Subtotal (95% CI)			**177**			**49**	**100.0%**	**0.73 [-2.27 , 3.73]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.48 (P = 0.63)								
7.4.5 False positive at baseline								
Aberle 2011	51.8	10.04	689	51.99	9.17	335	100.0%	-0.19 [-1.43 , 1.05]
Subtotal (95% CI)			**689**			**335**	**100.0%**	**-0.19 [-1.43 , 1.05]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.30 (P = 0.76)								
7.4.6 False positive at 6 months								
Aberle 2011	50.42	11.26	489	51.44	9.79	214	100.0%	-1.02 [-2.67 , 0.63]
Subtotal (95% CI)			**489**			**214**	**100.0%**	**-1.02 [-2.67 , 0.63]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.21 (P = 0.23)								
7.4.7 True positive at baseline								
Aberle 2011	52.03	11.04	41	53.77	8.57	22	100.0%	-1.74 [-6.66 , 3.18]
Subtotal (95% CI)			**41**			**22**	**100.0%**	**-1.74 [-6.66 , 3.18]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.69 (P = 0.49)								
7.4.8 True positive at 6 months								
Aberle 2011	46.3	13.65	29	46.22	12.17	13	100.0%	0.08 [-8.19 , 8.35]
Subtotal (95% CI)			**29**			**13**	**100.0%**	**0.08 [-8.19 , 8.35]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.02 (P = 0.98)								



Analysis 7.5. Comparison 7: Secondary outcome: health-related quality of life, Outcome 5: Anxiety by different results at 1 and 6 months



Comparison 8. Secondary outcome: lung cancer by stages at different time points

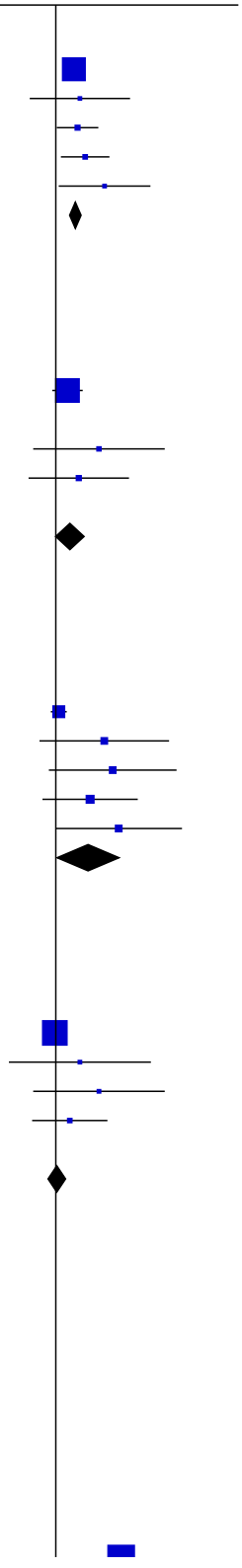
Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
8.1 baseline	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
8.1.1 stage 1 (A+B)	5	64092	Risk Ratio (M-H, Random, 95% CI)	2.41 [1.86, 3.12]
8.1.2 stage 2 (A+B)	5	64092	Risk Ratio (M-H, Random, 95% CI)	1.88 [0.99, 3.58]
8.1.3 stage 3 (A+B)	5	64092	Risk Ratio (M-H, Random, 95% CI)	4.28 [1.06, 17.27]
8.1.4 stage 4	5	64092	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.70, 1.55]
8.1.5 SCLC - limited	1	4104	Risk Ratio (M-H, Random, 95% CI)	Not estimable
8.1.6 SCLC - extensive	1	4104	Risk Ratio (M-H, Random, 95% CI)	19.00 [1.11, 326.23]
8.1.7 unknown	2	56773	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.31, 3.13]
8.2 at 1 year	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.2.1 stage 1 (A+B)	3	60877	Risk Ratio (M-H, Random, 95% CI)	2.57 [1.24, 5.32]
8.2.2 stage 2 (A+B)	3	60877	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.68, 2.84]
8.2.3 stage 3 (A+B)	3	60877	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.76, 1.95]
8.2.4 stage 4	3	60877	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.30, 0.77]
8.2.5 SCLC - limited	1	4104	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.06, 15.98]
8.2.6 SCLC - extensive	1	4104	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.12, 73.60]
8.2.7 unknown	2	56773	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.17, 10.75]
8.3 At year 2	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.3.1 stage 1 (A+B)	2	57559	Risk Ratio (M-H, Random, 95% CI)	3.53 [1.66, 7.53]
8.3.2 stage 2 (A+B)	2	57559	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.49, 2.37]
8.3.3 stage 3 (A+B)	2	57559	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.59, 1.44]
8.3.4 stage 4	2	57559	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.52, 1.24]
8.3.5 SCLC - limited	1	4104	Risk Ratio (M-H, Random, 95% CI)	Not estimable
8.3.6 SCLC - extensive	1	4104	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.01, 2.76]
8.3.7 unknown	1	53455	Risk Ratio (M-H, Random, 95% CI)	7.00 [0.86, 56.91]
8.4 5 to < 10 years	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.4.1 stage 1 (A+B)	4	13676	Risk Ratio (M-H, Random, 95% CI)	2.26 [1.43, 3.57]
8.4.2 stage 2 (A+B)	4	13676	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.37, 1.66]
8.4.3 stage 3 (A+B)	4	13676	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.47, 1.49]

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
8.4.4 4	4	13676	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.34, 0.91]
8.4.5 unknown	4	13676	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.41, 1.12]
8.5 ≥ 10 years	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.5.1 stage 1 (A+B)	4	64864	Risk Ratio (M-H, Random, 95% CI)	2.57 [1.36, 4.84]
8.5.2 stage 2 (A+B)	4	64864	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.76, 1.17]
8.5.3 stage 3 (A+B)	4	64864	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.79, 1.93]
8.5.4 stage 4	4	64864	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.69, 0.86]
8.5.5 unknown	3	60765	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.45, 0.99]

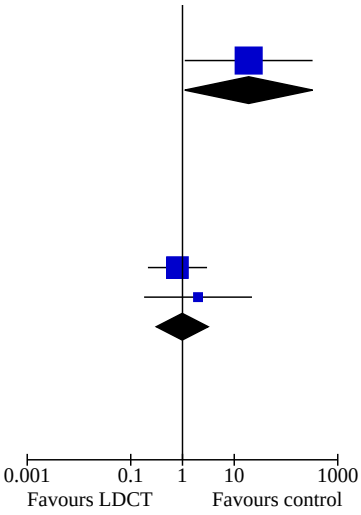
Analysis 8.1. Comparison 8: Secondary outcome: lung cancer by stages at different time points, Outcome 1: baseline

Study or Subgroup	LDCT Events	LDCT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
8.1.1 stage 1 (A+B)						
Aberle 2011	158	26722	70	26733	84.0%	2.26 [1.71 , 2.99]
Blanchon 2007	3	385	1	380	1.3%	2.96 [0.31 , 28.34]
Gohagan 2005	16	1660	6	1658	7.6%	2.66 [1.04 , 6.79]
Infante 2015	16	1264	4	1186	5.6%	3.75 [1.26 , 11.19]
Wille 2016	9	2052	1	2052	1.6%	9.00 [1.14 , 70.97]
Subtotal (95% CI)		**32083**		**32009**	**100.0%**	**2.41 [1.86 , 3.12]**
Total events:	202		82			
Heterogeneity: Tau² = 0.00; Chi² = 2.49, df = 4 (P = 0.65); I² = 0%						
Test for overall effect: Z = 6.70 (P < 0.00001)						
8.1.2 stage 2 (A+B)						
Aberle 2011	22	26722	13	26733	87.3%	1.69 [0.85 , 3.36]
Blanchon 2007	0	385	0	380		Not estimable
Gohagan 2005	3	1660	0	1658	4.7%	6.99 [0.36 , 135.25]
Infante 2015	3	1264	1	1186	8.0%	2.81 [0.29 , 27.02]
Wille 2016	0	2052	0	2052		Not estimable
Subtotal (95% CI)		**32083**		**32009**	**100.0%**	**1.88 [0.99 , 3.58]**
Total events:	28		14			
Heterogeneity: Tau² = 0.00; Chi² = 0.98, df = 2 (P = 0.61); I² = 0%						
Test for overall effect: Z = 1.94 (P = 0.05)						
8.1.3 stage 3 (A+B)						
Aberle 2011	64	26722	56	26733	36.7%	1.14 [0.80 , 1.64]
Blanchon 2007	4	385	0	380	14.2%	8.88 [0.48 , 164.43]
Gohagan 2005	6	1660	0	1658	14.5%	12.98 [0.73 , 230.30]
Infante 2015	5	1264	1	1186	19.9%	4.69 [0.55 , 40.10]
Wille 2016	8	2052	0	2052	14.6%	17.00 [0.98 , 294.34]
Subtotal (95% CI)		**32083**		**32009**	**100.0%**	**4.28 [1.06 , 17.27]**
Total events:	87		57			
Heterogeneity: Tau² = 1.35; Chi² = 9.72, df = 4 (P = 0.05); I² = 59%						
Test for overall effect: Z = 2.04 (P = 0.04)						
8.1.4 stage 4						
Aberle 2011	44	26722	46	26733	91.3%	0.96 [0.63 , 1.45]
Blanchon 2007	1	385	0	380	1.5%	2.96 [0.12 , 72.46]
Gohagan 2005	3	1660	0	1658	1.8%	6.99 [0.36 , 135.25]
Infante 2015	4	1264	2	1186	5.4%	1.88 [0.34 , 10.23]
Wille 2016	0	2052	0	2052		Not estimable
Subtotal (95% CI)		**32083**		**32009**	**100.0%**	**1.05 [0.70 , 1.55]**
Total events:	52		48			
Heterogeneity: Tau² = 0.00; Chi² = 2.64, df = 3 (P = 0.45); I² = 0%						
Test for overall effect: Z = 0.22 (P = 0.82)						
8.1.5 SCLC - limited						
Wille 2016	0	2052	0	2052		Not estimable
Subtotal (95% CI)		**2052**		**2052**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
8.1.6 SCLC - extensive						
Wille 2016	9	2052	0	2052	100.0%	19.00 [1.11 , 326.23]



Analysis 8.1. (Continued)

8.1.6 SCLC - extensive						
Wille 2016	9	2052	0	2052	100.0%	19.00 [1.11 , 326.23]
Subtotal (95% CI)		**2052**		**2052**	**100.0%**	**19.00 [1.11 , 326.23]**
Total events:	9		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.03 (P = 0.04)						
8.1.7 unknown						
Aberle 2011	4	26722	5	26733	76.9%	0.80 [0.21 , 2.98]
Gohagan 2005	2	1660	1	1658	23.1%	2.00 [0.18 , 22.01]
Subtotal (95% CI)		**28382**		**28391**	**100.0%**	**0.99 [0.31 , 3.13]**
Total events:	6		6			
Heterogeneity: Tau² = 0.00; Chi² = 0.43, df = 1 (P = 0.51); I² = 0%						
Test for overall effect: Z = 0.02 (P = 0.98)						



Analysis 8.2. Comparison 8: Secondary outcome: lung cancer by stages at different time points, Outcome 2: at 1 year

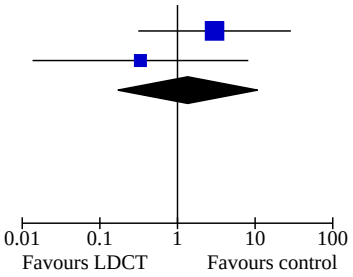
Study or Subgroup	LDCT Events	LDCT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
8.2.1 stage 1 (A+B)						
Aberle 2011	109	26722	42	26733	81.8%	2.60 [1.82 , 3.70]
Gohagan 2005	2	1660	2	1658	12.1%	1.00 [0.14 , 7.08]
Wille 2016	7	2052	0	2052	6.1%	15.00 [0.86 , 262.46]
Subtotal (95% CI)		**30434**		**30443**	**100.0%**	**2.57 [1.24 , 5.32]**
Total events:	118		44			
Heterogeneity: Tau² = 0.14; Chi² = 2.38, df = 2 (P = 0.30); I² = 16%						
Test for overall effect: Z = 2.54 (P = 0.01)						
8.2.2 stage 2 (A+B)						
Aberle 2011	18	26722	12	26733	95.0%	1.50 [0.72 , 3.11]
Gohagan 2005	0	1660	1	1658	5.0%	0.33 [0.01 , 8.17]
Wille 2016	0	2052	0	2052		Not estimable
Subtotal (95% CI)		**30434**		**30443**	**100.0%**	**1.39 [0.68 , 2.84]**
Total events:	18		13			
Heterogeneity: Tau² = 0.00; Chi² = 0.81, df = 1 (P = 0.37); I² = 0%						
Test for overall effect: Z = 0.91 (P = 0.36)						
8.2.3 stage 3 (A+B)						
Aberle 2011	33	26722	26	26733	83.4%	1.27 [0.76 , 2.12]
Gohagan 2005	5	1660	4	1658	12.8%	1.25 [0.34 , 4.64]
Wille 2016	1	2052	2	2052	3.8%	0.50 [0.05 , 5.51]
Subtotal (95% CI)		**30434**		**30443**	**100.0%**	**1.22 [0.76 , 1.95]**
Total events:	39		32			
Heterogeneity: Tau² = 0.00; Chi² = 0.56, df = 2 (P = 0.76); I² = 0%						
Test for overall effect: Z = 0.84 (P = 0.40)						
8.2.4 stage 4						
Aberle 2011	24	26722	52	26733	94.3%	0.46 [0.28 , 0.75]
Gohagan 2005	1	1660	1	1658	2.9%	1.00 [0.06 , 15.95]
Wille 2016	1	2052	1	2052	2.9%	1.00 [0.06 , 15.98]
Subtotal (95% CI)		**30434**		**30443**	**100.0%**	**0.48 [0.30 , 0.77]**
Total events:	26		54			
Heterogeneity: Tau² = 0.00; Chi² = 0.56, df = 2 (P = 0.75); I² = 0%						
Test for overall effect: Z = 3.04 (P = 0.002)						
8.2.5 SCLC - limited						
Wille 2016	1	2052	1	2052	100.0%	1.00 [0.06 , 15.98]
Subtotal (95% CI)		**2052**		**2052**	**100.0%**	**1.00 [0.06 , 15.98]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
8.2.6 SCLC - extensive						
Wille 2016	1	2052	0	2052	100.0%	3.00 [0.12 , 73.60]
Subtotal (95% CI)		**2052**		**2052**	**100.0%**	**3.00 [0.12 , 73.60]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.67 (P = 0.50)						
8.2.7 unknown						
Aberle 2011	3	26722	1	26733	63.8%	3.00 [0.31 , 28.85]
Gohagan 2005	0	1660	1	1658	36.2%	0.33 [0.01 , 8.17]

Analysis 8.2. (Continued)

Aberle 2011	3	26722	1	26733	63.8%	3.00 [0.31 , 28.85]
Gohagan 2005	0	1660	1	1658	36.2%	0.33 [0.01 , 8.17]
Subtotal (95% CI)		**28382**		**28391**	**100.0%**	**1.35 [0.17 , 10.75]**
Total events:	3		2			

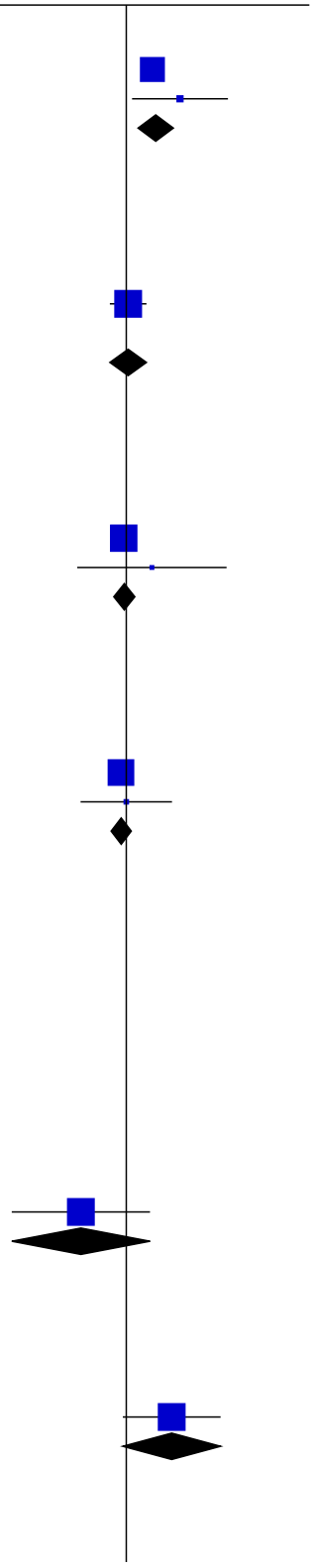
Heterogeneity: $Tau^2 = 0.42$; $Chi^2 = 1.21$, df = 1 (P = 0.27); $I^2 = 17\%$

Test for overall effect: Z = 0.29 (P = 0.77)



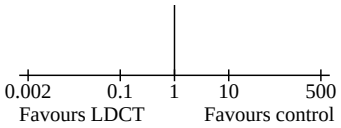
Analysis 8.3. Comparison 8: Secondary outcome: lung cancer by stages at different time points, Outcome 3: At year 2

Study or Subgroup	LDCT Events	LDCT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
8.3.1 stage 1 (A+B)						
Aberle 2011	147	26722	48	26733	88.0%	3.06 [2.21 , 4.24]
Wille 2016	10	2052	1	2052	12.0%	10.00 [1.28 , 78.05]
Subtotal (95% CI)		**28774**		**28785**	**100.0%**	**3.53 [1.66 , 7.53]**
Total events:	157		49			
Heterogeneity: Tau² = 0.14; Chi² = 1.25, df = 1 (P = 0.26); I² = 20%						
Test for overall effect: Z = 3.27 (P = 0.001)						
8.3.2 stage 2 (A+B)						
Aberle 2011	13	26722	12	26733	100.0%	1.08 [0.49 , 2.37]
Wille 2016	0	2052	0	2052		Not estimable
Subtotal (95% CI)		**28774**		**28785**	**100.0%**	**1.08 [0.49 , 2.37]**
Total events:	13		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.20 (P = 0.84)						
8.3.3 stage 3 (A+B)						
Aberle 2011	35	26722	39	26733	98.0%	0.90 [0.57 , 1.42]
Wille 2016	1	2052	0	2052	2.0%	3.00 [0.12 , 73.60]
Subtotal (95% CI)		**28774**		**28785**	**100.0%**	**0.92 [0.59 , 1.44]**
Total events:	36		39			
Heterogeneity: Tau² = 0.00; Chi² = 0.54, df = 1 (P = 0.46); I² = 0%						
Test for overall effect: Z = 0.36 (P = 0.72)						
8.3.4 stage 4						
Aberle 2011	35	26722	44	26733	95.1%	0.80 [0.51 , 1.24]
Wille 2016	2	2052	2	2052	4.9%	1.00 [0.14 , 7.09]
Subtotal (95% CI)		**28774**		**28785**	**100.0%**	**0.80 [0.52 , 1.24]**
Total events:	37		46			
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%						
Test for overall effect: Z = 0.98 (P = 0.32)						
8.3.5 SCLC - limited						
Wille 2016	0	2052	0	2052		Not estimable
Subtotal (95% CI)		**2052**		**2052**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
8.3.6 SCLC - extensive						
Wille 2016	0	2052	3	2052	100.0%	0.14 [0.01 , 2.76]
Subtotal (95% CI)		**2052**		**2052**	**100.0%**	**0.14 [0.01 , 2.76]**
Total events:	0		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.29 (P = 0.20)						
8.3.7 unknown						
Aberle 2011	7	26722	1	26733	100.0%	7.00 [0.86 , 56.91]
Subtotal (95% CI)		**26722**		**26733**	**100.0%**	**7.00 [0.86 , 56.91]**
Total events:	7		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.82 (P = 0.07)						



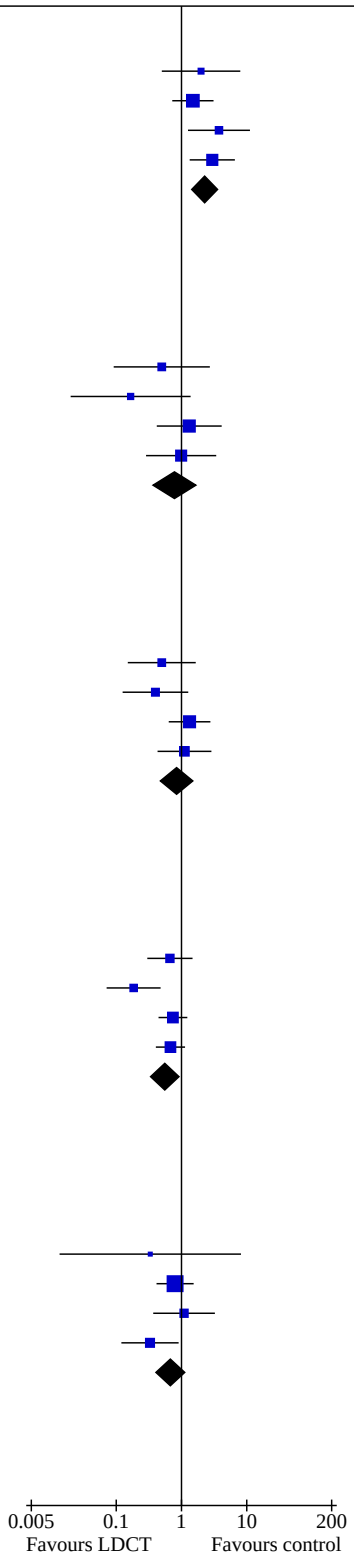
Analysis 8.3. (Continued)

Test for overall effect: Z = 1.82 (P = 0.07)

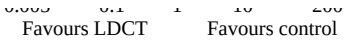


Analysis 8.4. Comparison 8: Secondary outcome: lung cancer by stages at different time points, Outcome 4: 5 to < 10 years

Study or Subgroup	LDCT Events	LDCT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
8.4.1 stage 1 (A+B)						
Becker 2020	6	2029	3	2023	10.8%	1.99 [0.50 , 7.96]
Field 2021	18	1987	12	1981	39.2%	1.50 [0.72 , 3.10]
Infante 2015	16	1264	4	1186	17.4%	3.75 [1.26 , 11.19]
Paci 2017	24	1613	8	1593	32.6%	2.96 [1.34 , 6.58]
Subtotal (95% CI)		**6893**		**6783**	**100.0%**	**2.26 [1.43 , 3.57]**
Total events:	64		27			
Heterogeneity: Tau² = 0.00; Chi² = 2.55, df = 3 (P = 0.47); I² = 0%						
Test for overall effect: Z = 3.51 (P = 0.0004)						
8.4.2 stage 2 (A+B)						
Becker 2020	2	2029	4	2023	18.4%	0.50 [0.09 , 2.72]
Field 2021	1	1987	6	1981	12.1%	0.17 [0.02 , 1.38]
Infante 2015	7	1264	5	1186	37.1%	1.31 [0.42 , 4.13]
Paci 2017	5	1613	5	1593	32.4%	0.99 [0.29 , 3.40]
Subtotal (95% CI)		**6893**		**6783**	**100.0%**	**0.78 [0.37 , 1.66]**
Total events:	15		20			
Heterogeneity: Tau² = 0.06; Chi² = 3.31, df = 3 (P = 0.35); I² = 9%						
Test for overall effect: Z = 0.64 (P = 0.52)						
8.4.3 stage 3 (A+B)						
Becker 2020	4	2029	8	2023	18.2%	0.50 [0.15 , 1.65]
Field 2021	4	1987	10	1981	19.3%	0.40 [0.13 , 1.27]
Infante 2015	17	1264	12	1186	36.5%	1.33 [0.64 , 2.77]
Paci 2017	9	1613	8	1593	26.0%	1.11 [0.43 , 2.87]
Subtotal (95% CI)		**6893**		**6783**	**100.0%**	**0.84 [0.47 , 1.49]**
Total events:	34		38			
Heterogeneity: Tau² = 0.09; Chi² = 4.11, df = 3 (P = 0.25); I² = 27%						
Test for overall effect: Z = 0.59 (P = 0.55)						
8.4.4 4						
Becker 2020	10	2029	15	2023	21.1%	0.66 [0.30 , 1.48]
Field 2021	5	1987	27	1981	17.2%	0.18 [0.07 , 0.48]
Infante 2015	26	1264	33	1186	31.0%	0.74 [0.44 , 1.23]
Paci 2017	24	1613	35	1593	30.7%	0.68 [0.40 , 1.13]
Subtotal (95% CI)		**6893**		**6783**	**100.0%**	**0.55 [0.34 , 0.91]**
Total events:	65		110			
Heterogeneity: Tau² = 0.14; Chi² = 6.92, df = 3 (P = 0.07); I² = 57%						
Test for overall effect: Z = 2.31 (P = 0.02)						
8.4.5 unknown						
Becker 2020	0	2029	1	2023	2.5%	0.33 [0.01 , 8.15]
Field 2021	16	1987	20	1981	52.9%	0.80 [0.41 , 1.53]
Infante 2015	7	1264	6	1186	20.8%	1.09 [0.37 , 3.25]
Paci 2017	5	1613	15	1593	23.9%	0.33 [0.12 , 0.90]
Subtotal (95% CI)		**6893**		**6783**	**100.0%**	**0.67 [0.41 , 1.12]**
Total events:	28		42			
Heterogeneity: Tau² = 0.02; Chi² = 3.15, df = 3 (P = 0.37); I² = 5%						
Test for overall effect: Z = 1.52 (P = 0.13)						

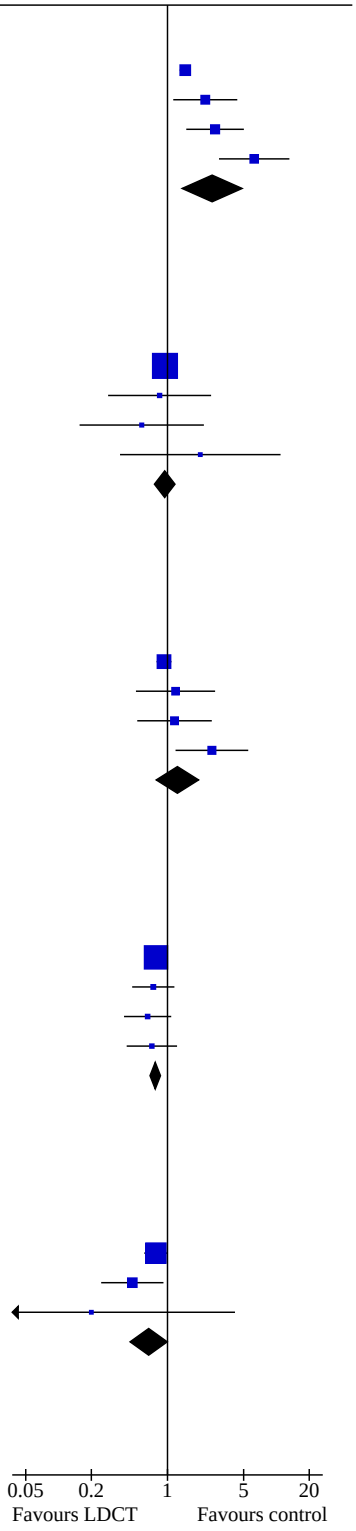


Analysis 8.4. (Continued)



Analysis 8.5. Comparison 8: Secondary outcome: lung cancer by stages at different time points, Outcome 5: ≥ 10 years

Study or Subgroup	LDCT Events	LDCT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
8.5.1 stage 1 (A+B)						
Aberle 2011	678	26722	466	26733	30.9%	1.46 [1.30 , 1.64]
Paci 2017	27	1613	12	1593	23.0%	2.22 [1.13 , 4.37]
Pastorino 2012	49	2376	13	1723	24.2%	2.73 [1.49 , 5.02]
Wille 2016	50	2052	8	2052	21.8%	6.25 [2.97 , 13.15]
Subtotal (95% CI)		**32763**		**32101**	**100.0%**	**2.57 [1.36 , 4.84]**
Total events:	804		499			
Heterogeneity: Tau² = 0.33; Chi² = 19.19, df = 3 (P = 0.0002); I² = 84%						
Test for overall effect: Z = 2.92 (P = 0.003)						
8.5.2 stage 2 (A+B)						
Aberle 2011	145	26722	153	26733	91.7%	0.95 [0.76 , 1.19]
Paci 2017	6	1613	7	1593	4.0%	0.85 [0.29 , 2.51]
Pastorino 2012	4	2376	5	1723	2.7%	0.58 [0.16 , 2.16]
Wille 2016	4	2052	2	2052	1.6%	2.00 [0.37 , 10.91]
Subtotal (95% CI)		**32763**		**32101**	**100.0%**	**0.94 [0.76 , 1.17]**
Total events:	159		167			
Heterogeneity: Tau² = 0.00; Chi² = 1.32, df = 3 (P = 0.72); I² = 0%						
Test for overall effect: Z = 0.53 (P = 0.59)						
8.5.3 stage 3 (A+B)						
Aberle 2011	298	26722	321	26733	43.8%	0.93 [0.79 , 1.09]
Paci 2017	12	1613	10	1593	17.7%	1.19 [0.51 , 2.74]
Pastorino 2012	16	2376	10	1723	19.0%	1.16 [0.53 , 2.55]
Wille 2016	23	2052	9	2052	19.6%	2.56 [1.19 , 5.51]
Subtotal (95% CI)		**32763**		**32101**	**100.0%**	**1.23 [0.79 , 1.93]**
Total events:	349		350			
Heterogeneity: Tau² = 0.11; Chi² = 6.81, df = 3 (P = 0.08); I² = 56%						
Test for overall effect: Z = 0.92 (P = 0.36)						
8.5.4 stage 4						
Aberle 2011	468	26722	597	26733	84.7%	0.78 [0.70 , 0.88]
Paci 2017	33	1613	44	1593	6.1%	0.74 [0.47 , 1.16]
Pastorino 2012	29	2376	32	1723	4.9%	0.66 [0.40 , 1.08]
Wille 2016	23	2052	32	2052	4.3%	0.72 [0.42 , 1.22]
Subtotal (95% CI)		**32763**		**32101**	**100.0%**	**0.77 [0.69 , 0.86]**
Total events:	553		705			
Heterogeneity: Tau² = 0.00; Chi² = 0.57, df = 3 (P = 0.90); I² = 0%						
Test for overall effect: Z = 4.60 (P < 0.00001)						
8.5.5 unknown						
Aberle 2011	112	26722	143	26733	72.1%	0.78 [0.61 , 1.00]
Paci 2017	13	1613	27	1593	26.3%	0.48 [0.25 , 0.92]
Wille 2016	0	2052	2	2052	1.6%	0.20 [0.01 , 4.16]
Subtotal (95% CI)		**30387**		**30378**	**100.0%**	**0.67 [0.45 , 0.99]**
Total events:	125		172			
Heterogeneity: Tau² = 0.04; Chi² = 2.65, df = 2 (P = 0.27); I² = 24%						
Test for overall effect: Z = 1.99 (P = 0.05)						

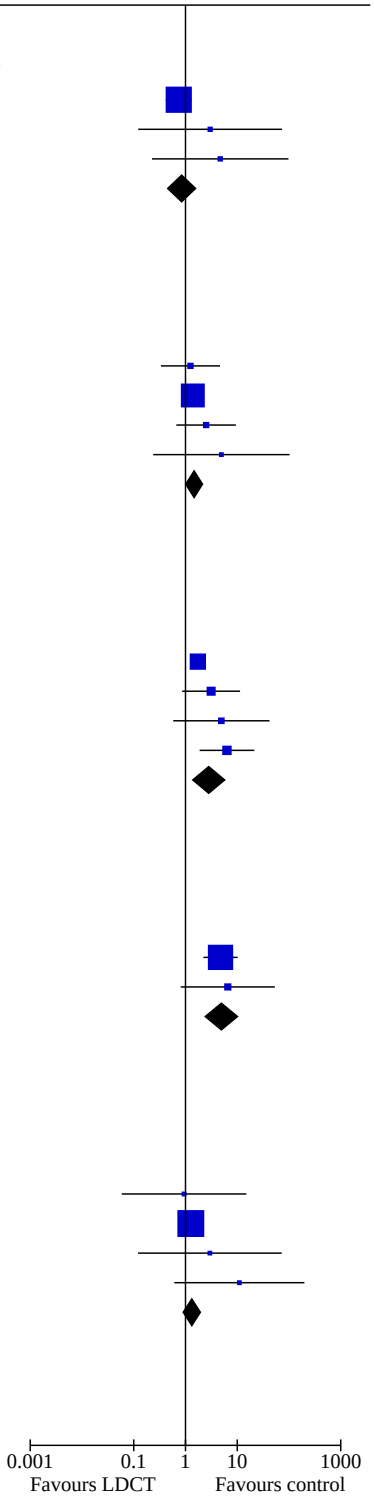


Comparison 9. Secondary outcome: lung cancer histology at different time points

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Histology types at baseline	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1.1 SCLC	4	59987	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.45, 1.57]
9.1.2 squamous cell carcinoma	4	59987	Risk Ratio (M-H, Random, 95% CI)	1.47 [1.01, 2.13]
9.1.3 adenocarcinoma	4	59987	Risk Ratio (M-H, Random, 95% CI)	2.81 [1.38, 5.71]
9.1.4 bronchoalveolar carcinoma	2	55904	Risk Ratio (M-H, Random, 95% CI)	4.94 [2.41, 10.10]
9.1.5 other	4	59987	Risk Ratio (M-H, Random, 95% CI)	1.32 [0.90, 1.94]
9.2 Histology at year 1	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.2.1 SCLC	1	3318	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.37, 10.89]
9.2.2 squamous cell carcinoma	1	3318	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.25, 2.72]
9.2.3 adenocarcinoma	1	3318	Risk Ratio (M-H, Random, 95% CI)	2.66 [1.24, 5.71]
9.2.4 other	1	3318	Risk Ratio (M-H, Random, 95% CI)	2.33 [0.60, 9.00]
9.3 Histology at follow-up	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.3.1 SCLC	6	71281	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.74, 1.01]
9.3.2 mixed SCLC + NSCLC	1	4104	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.01, 2.76]
9.3.3 squamous cell carcinoma	6	71281	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.81, 1.32]
9.3.4 adenocarcinoma	7	75333	Risk Ratio (M-H, Random, 95% CI)	1.49 [1.05, 2.10]
9.3.5 bronchoalveolar carcinoma	3	61610	Risk Ratio (M-H, Random, 95% CI)	2.73 [1.96, 3.81]
9.3.6 other	7	75333	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.68, 1.11]

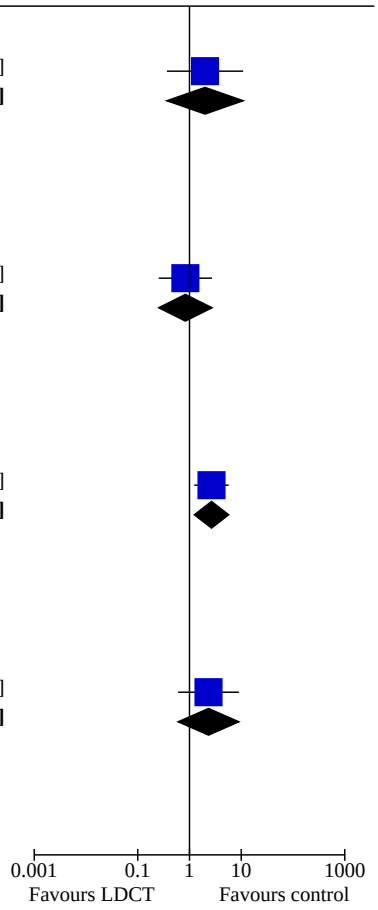
Analysis 9.1. Comparison 9: Secondary outcome: lung cancer histology at different time points, Outcome 1: Histology types at baseline

Study or Subgroup	LDCT Events	LDCT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
9.1.1 SCLC						
Blanchon 2007	0	385	0	380		Not estimable
Aberle 2011	20	26722	27	26732	92.1%	0.74 [0.42 , 1.32]
Gohagan 2005	1	1660	0	1658	3.7%	3.00 [0.12 , 73.50]
Infante 2015	2	1264	0	1186	4.1%	4.69 [0.23 , 97.62]
Subtotal (95% CI)		**30031**		**29956**	**100.0%**	**0.84 [0.45 , 1.57]**
Total events:	23		27			
Heterogeneity: Tau² = 0.02; Chi² = 2.03, df = 2 (P = 0.36); I² = 2%						
Test for overall effect: Z = 0.54 (P = 0.59)						
9.1.2 squamous cell carcinoma						
Gohagan 2005	5	1660	4	1658	8.1%	1.25 [0.34 , 4.64]
Aberle 2011	54	26722	39	26732	82.4%	1.39 [0.92 , 2.09]
Infante 2015	8	1264	3	1186	8.0%	2.50 [0.67 , 9.41]
Blanchon 2007	2	385	0	380	1.5%	4.94 [0.24 , 102.46]
Subtotal (95% CI)		**30031**		**29956**	**100.0%**	**1.47 [1.01 , 2.13]**
Total events:	69		46			
Heterogeneity: Tau² = 0.00; Chi² = 1.38, df = 3 (P = 0.71); I² = 0%						
Test for overall effect: Z = 2.01 (P = 0.04)						
9.1.3 adenocarcinoma						
Aberle 2011	123	26722	71	26732	50.3%	1.73 [1.29 , 2.32]
Infante 2015	10	1264	3	1186	19.6%	3.13 [0.86 , 11.34]
Blanchon 2007	5	385	1	380	9.1%	4.94 [0.58 , 42.04]
Gohagan 2005	19	1660	3	1658	21.0%	6.33 [1.88 , 21.34]
Subtotal (95% CI)		**30031**		**29956**	**100.0%**	**2.81 [1.38 , 5.71]**
Total events:	157		78			
Heterogeneity: Tau² = 0.24; Chi² = 5.53, df = 3 (P = 0.14); I² = 46%						
Test for overall effect: Z = 2.85 (P = 0.004)						
9.1.4 bronchoalveolar carcinoma						
Aberle 2011	38	26722	8	26732	88.3%	4.75 [2.22 , 10.18]
Infante 2015	7	1264	1	1186	11.7%	6.57 [0.81 , 53.30]
Subtotal (95% CI)		**27986**		**27918**	**100.0%**	**4.94 [2.41 , 10.10]**
Total events:	45		9			
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.78); I² = 0%						
Test for overall effect: Z = 4.37 (P < 0.0001)						
9.1.5 other						
Infante 2015	1	1264	1	1186	1.9%	0.94 [0.06 , 14.98]
Aberle 2011	57	26722	45	26732	95.0%	1.27 [0.86 , 1.87]
Blanchon 2007	1	385	0	380	1.4%	2.96 [0.12 , 72.46]
Gohagan 2005	5	1660	0	1658	1.7%	10.99 [0.61 , 198.53]
Subtotal (95% CI)		**30031**		**29956**	**100.0%**	**1.32 [0.90 , 1.94]**
Total events:	64		46			
Heterogeneity: Tau² = 0.00; Chi² = 2.45, df = 3 (P = 0.48); I² = 0%						
Test for overall effect: Z = 1.44 (P = 0.15)						



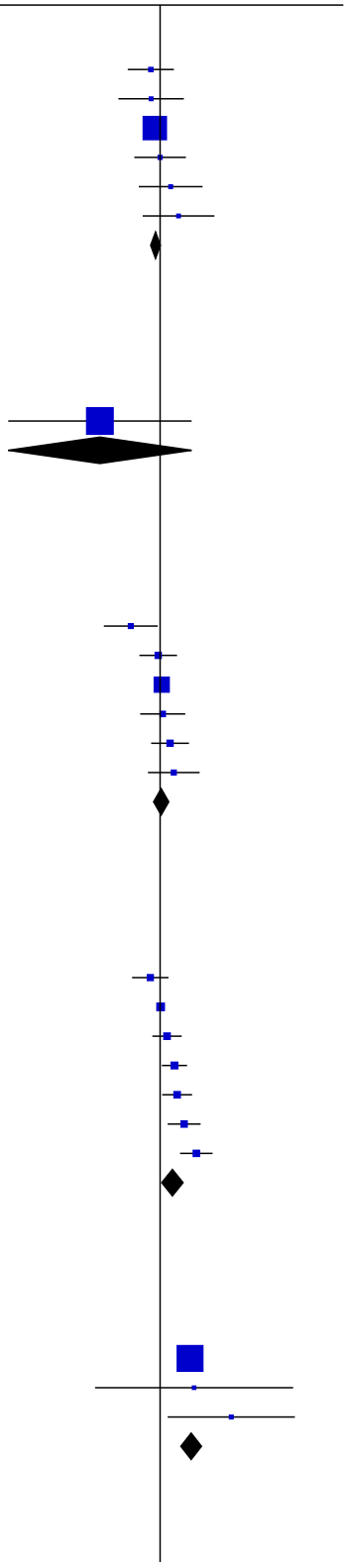
Analysis 9.2. Comparison 9: Secondary outcome: lung cancer histology at different time points, Outcome 2: Histology at year 1

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
9.2.1 SCLC						
Gohagan 2005	4	1660	2	1658	100.0%	2.00 [0.37 , 10.89]
Subtotal (95% CI)		**1660**		**1658**	**100.0%**	**2.00 [0.37 , 10.89]**
Total events:	4		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.80 (P = 0.42)						
9.2.2 squamous cell carcinoma						
Gohagan 2005	5	1660	6	1658	100.0%	0.83 [0.25 , 2.72]
Subtotal (95% CI)		**1660**		**1658**	**100.0%**	**0.83 [0.25 , 2.72]**
Total events:	5		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.30 (P = 0.76)						
9.2.3 adenocarcinoma						
Gohagan 2005	24	1660	9	1658	100.0%	2.66 [1.24 , 5.71]
Subtotal (95% CI)		**1660**		**1658**	**100.0%**	**2.66 [1.24 , 5.71]**
Total events:	24		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.52 (P = 0.01)						
9.2.4 other						
Gohagan 2005	7	1660	3	1658	100.0%	2.33 [0.60 , 9.00]
Subtotal (95% CI)		**1660**		**1658**	**100.0%**	**2.33 [0.60 , 9.00]**
Total events:	7		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.23 (P = 0.22)						



Analysis 9.3. Comparison 9: Secondary outcome: lung cancer histology at different time points, Outcome 3: Histology at follow-up

Study or Subgroup	LDCT Events	LDCT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
9.3.1 SCLC						
Paci 2017	12	1613	16	1593	4.4%	0.74 [0.35 , 1.56]
Field 2021	6	1987	8	1981	2.2%	0.75 [0.26 , 2.15]
Aberle 2011	245	26722	291	26732	85.7%	0.84 [0.71 , 1.00]
Wille 2016	11	2052	11	2052	3.5%	1.00 [0.43 , 2.30]
Infante 2015	9	1264	6	1186	2.3%	1.41 [0.50 , 3.94]
Pastorino 2012	10	2376	4	1723	1.8%	1.81 [0.57 , 5.77]
Subtotal (95% CI)		**36014**		**35267**	**100.0%**	**0.86 [0.74 , 1.01]**
Total events:	293		336			
Heterogeneity: Tau² = 0.00; Chi² = 2.88, df = 5 (P = 0.72); I² = 0%						
Test for overall effect: Z = 1.85 (P = 0.06)						
9.3.2 mixed SCLC + NSCLC						
Wille 2016	0	2052	3	2052	100.0%	0.14 [0.01 , 2.76]
Subtotal (95% CI)		**2052**		**2052**	**100.0%**	**0.14 [0.01 , 2.76]**
Total events:	0		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.29 (P = 0.20)						
9.3.3 squamous cell carcinoma						
Field 2021	7	1987	18	1981	6.9%	0.39 [0.16 , 0.93]
Paci 2017	20	1613	21	1593	12.7%	0.94 [0.51 , 1.73]
Aberle 2011	416	26722	395	26732	50.8%	1.05 [0.92 , 1.21]
Pastorino 2012	18	2376	12	1723	9.5%	1.09 [0.53 , 2.25]
Infante 2015	25	1264	17	1186	12.6%	1.38 [0.75 , 2.54]
Wille 2016	14	2052	9	2052	7.5%	1.56 [0.67 , 3.59]
Subtotal (95% CI)		**36014**		**35267**	**100.0%**	**1.04 [0.81 , 1.32]**
Total events:	500		472			
Heterogeneity: Tau² = 0.03; Chi² = 6.79, df = 5 (P = 0.24); I² = 26%						
Test for overall effect: Z = 0.28 (P = 0.78)						
9.3.4 adenocarcinoma						
Field 2021	19	1987	26	1981	12.2%	0.73 [0.40 , 1.31]
Aberle 2011	608	26722	598	26732	18.7%	1.02 [0.91 , 1.14]
Paci 2017	38	1613	30	1593	14.0%	1.25 [0.78 , 2.01]
Becker 2020	59	2029	37	2023	15.0%	1.59 [1.06 , 2.39]
Pastorino 2012	55	2376	23	1723	13.8%	1.73 [1.07 , 2.81]
Infante 2015	44	1264	19	1186	13.1%	2.17 [1.28 , 3.70]
Wille 2016	58	2052	18	2052	13.2%	3.22 [1.91 , 5.45]
Subtotal (95% CI)		**38043**		**37290**	**100.0%**	**1.49 [1.05 , 2.10]**
Total events:	881		751			
Heterogeneity: Tau² = 0.16; Chi² = 32.60, df = 6 (P < 0.0001); I² = 82%						
Test for overall effect: Z = 2.26 (P = 0.02)						
9.3.5 bronchoalveolar carcinoma						
Aberle 2011	121	26722	46	26732	96.3%	2.63 [1.87 , 3.69]
Wille 2016	1	2052	0	2052	1.1%	3.00 [0.12 , 73.60]
Becker 2020	10	2029	1	2023	2.6%	9.97 [1.28 , 77.81]
Subtotal (95% CI)		**30803**		**30807**	**100.0%**	**2.73 [1.96 , 3.81]**
Total events:	132		47			
Heterogeneity: Tau² = 0.00; Chi² = 1.59, df = 2 (P = 0.45); I² = 0%						
Test for overall effect: Z = 5.91 (P < 0.00001)						



Analysis 9.3. (Continued)

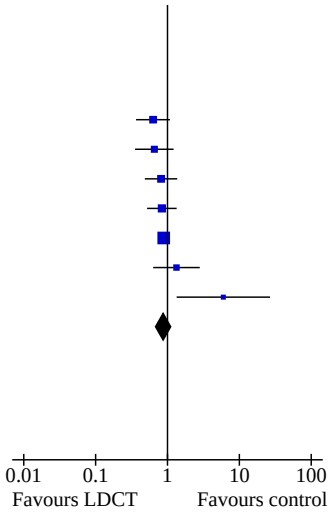
Test for overall effect: Z = 5.91 (P < 0.00001)

9.3.6 other						
Paci 2017	21	1613	33	1593	13.3%	0.63 [0.37 , 1.08]
Pastorino 2012	19	2376	21	1723	11.1%	0.66 [0.35 , 1.22]
Infante 2015	26	1264	30	1186	14.1%	0.81 [0.48 , 1.37]
Becker 2020	31	2029	37	2023	15.9%	0.84 [0.52 , 1.34]
Aberle 2011	311	26722	351	26732	34.8%	0.89 [0.76 , 1.03]
Wille 2016	16	2052	12	2052	8.3%	1.33 [0.63 , 2.81]
Field 2021	12	1987	2	1981	2.5%	5.98 [1.34 , 26.69]
Subtotal (95% CI)		**38043**		**37290**	**100.0%**	**0.87 [0.68 , 1.11]**
Total events:	436		486			

Heterogeneity: Tau² = 0.04; Chi² = 9.99, df = 6 (P = 0.12); I² = 40%

Test for overall effect: Z = 1.14 (P = 0.26)

Test for subgroup differences: Chi² = 45.77, df = 5 (P < 0.00001), I² = 89.1%



Comparison 10. Secondary outcome: other outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 contamination	3	6902	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.32, 5.68]

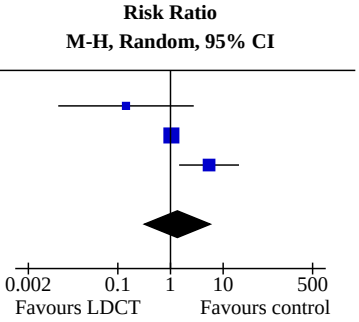
Analysis 10.1. Comparison 10: Secondary outcome: other outcomes, Outcome 1: contamination

Study or Subgroup	LDCT Events	LDCT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Wille 2016	0	2052	3	2052	15.9%	0.14 [0.01 , 2.76]
Infante 2015	307	1264	277	1186	49.1%	1.04 [0.90 , 1.20]
Gohagan 2005	8	115	3	233	35.0%	5.40 [1.46 , 19.98]
Total (95% CI)		**3431**		**3471**	**100.0%**	**1.35 [0.32 , 5.68]**
Total events:	315		283			

Heterogeneity: Tau² = 1.09; Chi² = 7.78, df = 2 (P = 0.02); I² = 74%

Test for overall effect: Z = 0.41 (P = 0.68)

Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Nodule management

	Interpretation	Management
Aberle 2011	Positive scan: findings suspicious of lung cancer, such as non-calcified nodule ≥ 4 mm, lung consolidation, or obstructive atelec-	No trial-wide algorithm

Table 1. Nodule management *(Continued)*

	tasis, nodule enlargement, and nodules with suspicious changes in attenuation	
Becker 2020	Positive scan: any nodule ≥ 5 mm	• No abnormality or nodule < 5 mm: routine screening • Nodules 5 mm to 7 mm: early recall (6 months) • Nodules 8 mm to 10 mm: earlier recall (3 months) • Nodules > 10 mm: immediate recall **On recall scans** • > 600 VDT: back to routine scans • 400 VDT to 600 VDT: 6 months early recall • < 7.5 mm: early recall 6 months • ≥ 7.5 mm to 10 mm: early recall at 3 months • ≤ 400 VDT or > 10 mm diameter: immediate recall
Blanchon 2007	Positive scan: non-calcified nodule > 5 mm	• Non-calcified nodule ≤ 5 mm: repeat LDCT in 1 year • Non-calcified nodule > 5 mm and < 10 mm: repeat LDCT in 3 months If no change: repeat scan at 6 months, 12 months and 24 months from baseline. If growth at any time: histological diagnosis. • Non-calcified nodule ≥ 10 mm: CT with contrast versus PET versus histological diagnosis discussed in MDM with pulmonary oncologist, radiologist and thoracic surgeon
De Koning 2020	Classification of non-calcified nodules: • NODCAT 1: benign nodule (fat/benign calcifications) or other benign characteristics • NODCAT 2: any nodule, smaller than NODCAT 3 and no characteristics of NODCAT 1 • NODCAT 3: solid (500 mm^3 to 500 mm^3), solid/pleural based (5 mm dmin to 10 mm dmin), partial solid/non-solid component (≥ 8 mm dmean), partial solid/solid component (50 mm^3 to 500 mm^3), non-solid (≥ 8 mm dmean) • NODCAT 4: solid (> 500 mm^3), solid/pleural based (> 10 mm dmin), partial solid/solid component (> 500 mm^3) Classification of nodules based on growth: • GROWCAT A: VDT > 600 days	**Management of non-calcified nodules based on baseline screening** • NODCAT 1: negative test, annual CT • NODCAT 2: negative test, annual CT • NODCAT 3: indeterminate test, 3-month follow-up CT • NODCAT 4: positive test, refer to pulmonologist for work up and diagnosis • GROWCAT: positive test, histological diagnosis **Management protocol for non-calcified nodules at incidence screening** • NODCAT 1: negative test, CT in year 4 • NODCAT 2: indeterminate test, CT in year 3 • NODCAT 3: indeterminate test, CT after 6-8 weeks • NODCAT 4: positive test, work up for work up and diagnosis • GROWCAT C- positive test, histological diagnosis required **At year 4** • NODCAT 1: negative test, CT in year 6 • NODCAT 2: indeterminate test, CT after 1 year • NODCAT 3: indeterminate test, CT after 6-8 weeks • NODCAT 4: positive test, refer to pulmonologist • GROWCAT A: negative test, CT in year 6

Table 1. Nodule management *(Continued)*

	• GROWCAT BL: VDT 400 days to 600 days • GROWCAT C: VDT< 400 days or a new solid component in a non-solid lesion	• GROWCAT B: indeterminate test, repeat CT after 1 year • GROWCAT C: positive test, refer to pulmonologist **At year 6** • NODCAT 1: negative test, end of screening • NODCAT 2: indeterminate test, end of screening • NODCAT 3: indeterminate test, CT after 6-8 weeks • NODCAT 4: positive test, refer to pulmonologist for work up and diagnosis • GROWCAT A: negative test, end of screening • GROWCAT B: indeterminate screening, CT after 1 year • GROWCAT C: positive test, refer to pulmonologist Preoperative biopsy was not routine. Suspicious nodules were removed by VATS or thoracotomy with wedge resection+frozen section. Lobectomies were performed only for central nodules that could not be approached by wedge resection. If cancer was diagnosed by VATS, the procedure was converted to an open thoracotomy with sampling of lobar, interlobar, hilar and mediastinal lymph nodes as VATS resection in lung cancer was not fully implemented at the time of trial in the Netherlands. Mediastinoscopy was performed before proceeding to VATS or thoracotomy in subjects with mediastinal lymph nodes > 10 mm in short axis and/or positive nodes.
Field 2021	Classification of nodules: • Cat 1: nodules containing fat or with a benign pattern of calcification are considered benign. Solid nodules < 15 mm^3 or if pleural or juxta pleural < 3 mm^3. • Cat 2: solid intraparenchymal nodules with a volume of 15 mm^3 to 49 mm^3. Pleural or juxta pleural nodules with a maximal diameter of 3.1 mm to 4.9mm. Part solid nodules with a maximal non-solid component of < 5 mm diameter or where the solid component volume is < 15 mm^3. • Cat 3: solid intraparenchymal nodules with a volume of 50 mm^3 to 500 mm^3. Pleural or juxtapleural nodules with a maximal diameter of 5 mm to 9.9 mm. Non-solid nodules with a maximal diameter of > 5 mm or part solid nodules where solid component volume is 15 mm^3 to 500 mm^3. • Cat 4: solid intraparenchymal nodules with a volume > 500	• Cat 1: nil further scans • Cat 2: follow-up CT in 1 year and assessed for VDT or new solid component in non-solid nodule • If no growth, stop follow-up • If growth, for MDT • Cat 3: follow-up CT in 3 months and assessed for VDT or new solid component in non-solid nodule. If no growth then CT in 9 months • If VDT > 400 days, stop follow-up • If VDT ≤ 400 days then MDT assessment • If growth then MDT assessment • 4. Cat 4: MDT assessment

Table 1. Nodule management *(Continued)*

	mm^3, pleural or juxtapleural nodules with a maximal diameter of ≥ 10 mm. Part solid nodules with a solid component with a volume > 500 mm^3.	
Gohagan 2005	• Positive scan: any non-calcified nodule ≥ 4 mm Other abnormalities could also be considered suspicious for lung cancer at the discretion of the radiologist.	No trial-wide algorithm for management • Telephone call to patient with positive test and urged to seek medical follow-up with additional follow-up calls at 4 weeks +/- 8 weeks if follow-up had not begun at the 4-week phone call • Referrals to specialists for follow-up of positive screening; results were provided if requested by the participant

Infante 2015	• Positive scan: non-calcified pulmonary nodules ≥ 10 mm in diameter or smaller but showing spiculated margins, or non-nodular lesions such as a hilar mass, focal ground glass opacities, major atelectasis, endobronchial lesions, mediastinal adenopathy, pleural effusion or pleural masses	No set trial-wide algorithm for management
		• If lesion smooth and < 10 mm in size: LDCT at 3, 6, and 12 months
		  ○ If no change occurs: follow-up after 1 year
		• Non-smooth lesion ≥ 6 mm but ≤ 10 mm: oral antibiotics and new HRCT after 6 to 8 weeks
		  ○ If no regression occurs: evaluation on a case-by-case basis as to the opportunity to follow the lesion or to perform invasive procedures to obtain a tissue diagnosis
		• Lesion ≥ 10 mm but ≤ 20 mm: oral antibiotics and new HRCT after 6 to 8 weeks
		  ○ If no regression occurs: PET. If PET is positive: tissue diagnosis. If PET is negative: close follow-up
		• Lesion ≥ 20 mm: discretional oral antibiotics and new HRCT or standard CT + PET
		  ○ If PET positive: tissue diagnosis
		  ○ If PET negative: close follow-up
		• Focal ground glass opacities: oral antibiotics and new HRCT after 6 to 8 weeks. Evaluation on case-by-case basis as to opportunity to follow lesion or obtain tissue diagnosis based on the size, number of lesions, location and ratio of any solid versus non-solid component

LaRocca 2002	• Positive scan: ≥ 5 mm nodule with suspicious features	• Abnormal mass > 10 mm in diameter or 5 mm to 10 mm in diameter and highly suspicious for malignancy: CXR and tissue diagnosis is obtained • If the abnormal mass ≤ 10 mm in diameter: thin section high resolution image of the mass is obtained • If this image is normal or benign, annual spiral CT scanning is continued. • If the image is indeterminate, a repeat high-resolution scan is performed in 3 months. • If the image is unchanged at 3 months, annual spiral CT scanning is continued. • If the mass is larger at 3 months: CXR and tissue diagnosis is performed.

Paci 2017	• Positive scan: at least one non-calcified nodule ≥ 5 mm or a non-solid nodule ≥ 10 mm or the presence of a part-solid nodule	• Solid non-calcified nodule ≥ 8mm and non-solid non-calcified nodule > 10 mm: PET
		  ○ If PET positive: FNA recommended (if FNA negative or indeterminate: 3 month follow-up scan)
		  ○ If PET negative: 3 month follow-up scan
		  ○ All cases with no nodule growth at follow-up exam were invited to annual repeat CT scan

Table 1. Nodule management *(Continued)*

		• Solid or part-solid non-calcified nodules with diameter between 5 mm to 7 mm: follow-up dose LDCT after 3 months
		  ○ If significant growth (increase ≥ 1 mm in mean diameter in a solid nodule or increase of solid component in a part solid nodule): considered potentially malignant
		  ○ If considered potentially malignant and peripheral nodule, FDG PET or CT-guided FNA arranged
		  ○ If considered potentially malignant and deep nodule, FDG PET or bronchoscopy arranged.
		  ○ Bronchoscopy also performed for airway abnormalities
		• If screening test revealed focal abnormalities consistent with inflammatory disease: antibiotic therapy and 1 month follow-up CT recommended
		• In case of complete resolution, the subject was sent to annual repeat screening
		• In case of partial or lack of resolution, further 2-month follow-up CT performed
		• All subjects with FNA evidence of malignancy underwent a staging CT (CT chest/abdominal/head and neck exam with IV contrast).

Pastorino 2012	• Negative nodule: non-calcified nodule < 60 mm^3 or nodules with fat or benign pattern of calcification • Indeterminate: non-calcified nodules 60 mm^3 to 250 mm^3 • Positive result: non-calcified nodules > 250 mm^3 • Positive result was also based on findings such as non-calcified hilar or mediastinal lymphadenopathy, atelectasis, consolidation, pleural findings	• Solid lesions < 60 mm^3 in volume (diameter ≥ 4.8 mm) considered: repeat LDCT for 1 or 2 years • Nodules with a volume of 60 mm^3 to 250 mm^3 (5 mm to 8 mm in diameter): underwent repeat CT exam after 3 months • Nodules with a volume > 250 mm^3: additional work-up including PET or lung biopsy • Volumetric growth was used on serial imaging with significant growth considered ≥ 25% after 3-month interval ○ If no growth, back to planned screening intervals • Ground glass opacities were conservatively managed.
Wille 2016	• Category 1: nodules ≤ 15 mm in maximal diameter with benign characteristics or ≤ 20 mm for calcified nodules • Category 2: nodules < 5 mm • Category 3: nodules 5 mm to 15 mm not classified as benign • Category 4: nodules > 15 mm or suspicious morphology • Category 5: growing nodules (increase in volume ≥ 25%)	• Category 1 and 2: nil further action • Category 3: indeterminate: repeat scan in 3 months • Category 4 and 5: diagnostic investigation

CT: computed tomography; **CXR**: chest x-ray; **dmean**: mean diameter; **dmin**: minimal diameter; **FDG PET**: fluorodeoxyglucose positron emission tomography; **FNA**: fine needle aspiration; **HRCT**; high-resolution computed tomography; **IV**: intravenous; **LDCT**: low-dose computed tomography; **MDM**: multidisciplinary meeting; **MDT**: multidisciplinary team; **PET**: positron emission tomography; **VATS**: video-assisted thoracoscopic surgery; **VDT**: volume doubling time.

Table 2. Invasive tests in non-lung cancer-related disease

	Invasive tests in non-lung cancer-related disease
Aberle 2011	*At 6.5 year follow-up* **LDCT group**: 457 procedures for non-lung cancer-related disease (164 thoracotomies/thoracoscopies/mediastinoscopies; 227 bronchoscopies; 66 needle biopsies) out of 17,053 positive screening results over 3 rounds with complete diagnostic information **CXR group**: 115 procedures for benign disease (45 thoracotomies/thoracoscopies/mediastinoscopies; 46 bronchoscopies; 24 needle biopsies) out of 4674 positive screening results over 3 rounds with complete information
Becker 2020	**Baseline LDCT**: 30 biopsies performed in benign disease (at least 5 thoracotomies, 2 VATS thoracoscopies, and 1 bronchoscopy) Year 1 LDCT: 19 biopsies performed in benign disease Year 2 LDCT: 12 biopsies performed in benign disease Year 3 LDCT: 16 biopsies performed in benign disease Year 4 LDCT: 13 biopsies performed in benign disease
Blanchon 2007	Trial arm not specified. Baseline: 3 thoracostomies performed for benign disease
De Koning 2020	**Baseline LDCT**: 27.2% of invasive procedures performed in benign disease Between 2004 and 2008: 215 participants had surgery. 2/17 mediastinoscopies were in benign diease; 47/198 lung surgeries (thoracotomies+/- VATS) were in benign disease.
Field 2021	**Baseline LDCT**: 7 participants had needle biopsies, 1 EBUS bronchoscopy, 4 referrals for surgery completed for benign disease
Gohagan 2005	**Baseline LDCT**: 16 bronchoscopies, 19 lung biopsies or resection, and 23 any invasive procedures (including biopsy/resection, bronchoscopy, thoracotomy, thoracoscopy, mediastinotomy, mediastinoscopy) performed for benign disease **Baseline CXR**: 5 bronchoscopies, 6 lung biopsies or resections, and 8 procedures (including biopsy/resection, bronchoscopy, thoracotomy, thoracoscopy, mediastinotomy, mediastinoscopy) performed for benign disease
Infante 2015	*At 8.35 years median follow-up* **LDCT group**: 17 surgeries for benign disease (3 mediastinoscopies, 7 VATS wedge resections, 6 open wedge resections, 1 open segmentectomy). 7 surgeries for other conditions (reported as 1 open biopsy, 1 extrapleural pneumonectomy for mesothelioma, 2 oesophagectomies for cancer, 1 oesophageal leiomyoma VATS resection, 2 VATS thymectomies, 1 lobectomy for aspergilloma) **Control arm**: 5 surgeries for benign disease (2 VATS biopsies, 2 VATS wedge resection, 1 open wedge resection); 2 surgeries for other conditions (1 open lung biopsy for hilar lymphoma, 1 VATS thymectomy)
LaRocca 2002	Not available
Paci 2017	**Baseline LDCT**: 1 FNA biopsy and 1 (5.5% of all surgical resections) surgical resection for benign disease reported
Pastorino 2012	**Median 6 annual LDCTs:** 1 invasive diagnostic procedure (transthoracic needle aspiration, fibro bronchoscopy, transbronchial needle aspiration), 0 anatomical (lobectomy or segmentectomy) resections, 0 non-anatomical resections (wedge resection) performed for benign disease

Table 2. Invasive tests in non-lung cancer-related disease *(Continued)*

	Median 3 biennial LDCTs: 3 invasive diagnostic procedures (transthoracic needle aspiration, fibro bronchoscopy, transbronchial needle aspiration), 0 anatomical (lobectomy or segmentectomy) resections, 1 non-anatomical resection (wedge resection) performed for benign disease
Wille 2016	**Baseline LDCT**: 1 mediastinoscopy, 3 bronchoscopy with biopsy, 1 EUS, 2 EBUS, 2 VATS, 1 percutaneous biopsy performed for benign disease

CXR: chest x-ray; **EBUS**: endobronchial ultrasound; **EUS:** endoscopic ultrasound; **FNA**: fine needle aspirate; **LDCT**: low-dose computed tomography; **VATS**: video-assisted thoracoscopic surgery

Table 3. Recall rates, false positives and overdiagnosis

	Recall rates at overall baseline LDCT recall rate = 18% (8078/44,920)	**False positives** **Overall false-positive rate from baseline LDCT = 21%** **(8874/41857)**	**Overdiagnosis**
Aberle 2011	All chest CTs performed postbaseline LDCT: 20% (5153/26,309) All chest CTs performed postbaseline CXR in control group: 6%	Baseline LDCT: 6911/26,309 (26%) Baseline CXR: 2243/26,035 (7%) 1-year LDCT: 6728/24715 (27%) 1-year CXR: 1416/24,089 (6%) 2-year LDCT: 3838/24,102 (16%) 2-year CXR: 1094/23, 346 (5%)	At 6.5 years post-randomisation: • 11% (95% CI 3.2 to 18.2) from a public health perspective and 18.5% (95% CI 5.4 to 30.6) from a clinical perspective of all lung cancers • 67.6% (95% CI 53.5 to 78.5) from a public health perspective and 78.9% (95% CI 62.2 to 93.5) from a clinical perspective of all BAC At 11.3 years post-randomisation: • 3.1% of all lung cancers and 79% of BAC from a public health perspective
Becker 2020	Baseline LDCT: 22% (451/2028) 1-year LDCT: 5% 2-year LDCT: 4% 3-year LDCT: 6% 4-year LDCT: 5%	Baseline LDCT: 426/2028 (21%) 1-year LDCT: 77/1892 (4%) 2-year LDCT: 62/1849 (3%) 3-year LDCT 94/1826 (5%) 4-year LDCT: 88/1810 (5%)	At 9.7 years post-randomisation: • 17.8% (95% CI -7.4 to 44.7) from a public health perspective and 25.4% (95% CI -11.3 to 64.3) from a clinical perspective of all lung cancers • 90% (95% CI 54.3 to 164.4) from a public health perspective and 112.5% (95% CI 68.2 to 113.1) from a clinical perspective of all BAC
Blanchon 2007	Not available	Baseline LDCT: 73/336 (22%) Baseline CXR: 14/285 (5%)	Not available
De Koning 2020	Baseline LDCT: 19% (1438/7557) 1-year LDCT: 19%	Baseline LDCT 107/7557 (1%) 1-year LDCT: 64/7295 (1%)	Not available

Table 3. Recall rates, false positives and overdiagnosis *(Continued)*

		3-year LDCT: 276/6922 (4%) 5.5-year LDCT: 62/5279 (1%)	
Field 2021	Baseline LDCT: 5% (103/1994)	Baseline LDCT: *909/1994 (46%) **72/1994 (4%) *when defined as needing any work-up **when defined as referred to MDT	Estimated 15% of all lung cancers
Gohagan 2005	Baseline LDCT: 15% (232/1586) Baseline CXR: 5% (76/1550) Overall post-LDCT: 8% Overall post-CXR in control group: 3%	Baseline LDCT: 286/1586 (18%) Baseline CXR: 139/1550 (9%)	Not available
Infante 2015	Baseline LDCT: 10% (128/1276)	Not available	Not available
LaRocca 2002	Not available	Not available	Not available
Paci 2017	Baseline LDCT: 23% 366/1406) 1-year LDCT: 14% 2-year LDCT: 13% 3-year LDCT: 11%	Not available	At 11.3 years post-randomisation, estimated overdiagnosis rates reported as -4% using public health perspective and -10% from a clinical perspective
Pastorino 2012	Baseline LDCT: 15% in annual group, 14% in (284/2303) biennial group 1-year LDCT: 3% in annual group, 3% in biennial group 2-year LDCT: 5% in annual group, 5% in biennial group 3-year LDCT: 3% in annual group, 7% in biennial group 4-year LDCT: 2% in annual group, 3% in biennial group 5-year LDCT: 1% in annual group, 7% in biennial group 6-year LDCT: 4% in annual group, 5% in biennial group	Median 6 annual LDCT: 54/1152 (5%) Median 3 biennial LDCT: 34/1151 (3%)	Not available
Wille 2016	Baseline LDCT: 8% (155/2047) 1-year LDCT: 1% 2-year LDCT: 1% 3-year LDCT: 1%	Baseline LDCT: 162/2047 (8%) 1-year LDCT: 34/1976 (2%) 2-year LDCT: 39/1944 (2%) 3-year LDCT: 32/1982 (2%)	Estimated 67.2% of lung cancers (95% CI 37.1 to 95.4) from unplanned posthoc analysis

Table 3. Recall rates, false positives and overdiagnosis *(Continued)*

	4-year LDCT: 1%	4-year LDCT: 35/1851 (2%)

BAC: bronchioalveolar carcinoma; **CI**: confidence interval; **CT**: computed tomography; **CXR**: chest x-ray; **LDCT**: low-dose computed tomography; **MDT**: multidisciplinary team.

Table 4. Response, adherence and contamination rates

	Response rates to recruitment	Adherence to screening	Contamination
Aberle 2011	Not available	Overall adherence to all 3 screening rounds: 95% of participants completed LDCT scan, 93% in the control group completed CXR	Not available
Becker 2020	• 292,440 people received questionnaires • 95,797 people responded • 4913 people met eligibility criteria • 4052 people were enrolled and randomised to the trial (1% of those who received a questionnaire, and 4% of respondents)	Baseline: almost 100% completed LDCT scan. 1-year: 95% completed LDCT scan. 2-year: 93% completed LDCT scan. 3-year: 93% completed LDCT scan. 4-year: 94% completed LDCT scan.	10 years postrandomisation: 264 participants in the control arm had received a CT.
Blanchon 2007	• 830 eligible people were approached • 765 people consented to be randomised (92% of eligible people)	Baseline: 86% participants completed LDCT scan, 75% in control arm completed CXR.	At baseline: 6 participants in the control arm inadvertently received a LDCT.
De Koning 2020	• 606,409 people received the first questionnaire • 150,920 responded to the questionnaire • 30,959 people were eligible and invited to participate • 15,822 people completed second questionnaire and were included and randomised (3% of people who received the first questionnaire and 51% of eligible respondents)	Baseline: 95% of participants completed LDCT scan 1 year: 97% of participants completed LDCT scan 3 years: 95% completed LDCT scan 5.5 years: 78% of participants completed LDCT scan	At 2 years: 3.6% of participants in the control arm had received CT for any reason
Field 2021	• 247,354 people invited to participate in study • 75,958 responded positively to invitations • 8729 of respondents assessed as high risk	Baseline: 98% of participants completed LDCT scan	Not available

Table 4. Response, adherence and contamination rates *(Continued)*

	• 5967 responded to second questionnaire • 4868 invited to recruitment centre • 4152 attended recruitment centre • 4061 consented to participation • 4055 randomised to trial (2% of those invited and 46% of high-risk respondents)		
Gohagan 2005	• 653,417 people mailed information packages • 12,270 people contacted screening centre and underwent eligibility assessment • 4828 people eligible for trial • 3409 people were randomised, however 91 participants subsequently found to be ineligible • 3318 participants randomised and included in analysis (1% of people who received mail packages and 27% who were screened for eligibility)	Baseline: 95% of participants completed LDCT scan, 93% of the control group completed CXR 1-year: 86% of participants completed LDCT scan, 80% of the control group completed CXR	Contamination assessed by random sample of participants At baseline: 5% of respondents in the intervention arm had received a CXR for medical or screening purposes. 0.9% of respondents in the control arm had received a CT for medical or screening purposes. At 1 year: 10% of participants in the intervention arm had received a CXR for medical or screening purposes and 1.3% of respondents in the control arm had received a CT for medical or screening purposes.
Infante 2015	Not available	Not available	3 years post-randomisation: • intervention arm (74 extra CT scan, 233 extra CXRs) • control arm (extra 68 CTs, 209 extra CXRs) Did not specify if for screening purposes, only outside protocol
LaRocca 2002	• 3418 people completed screening questionnaires • 904 participants completed prescreening baseline CXR • 871 participants randomised to trial (25% of people who completed screening questionnaire)	Not available	Not available
Paci 2017	• 71232 people sent letters • 17,055 people responded to letters • 3206 people were eligible and randomised (5% of people who received letters and 19% of respondents)	Baseline: 87% completed LDCT scan 1 year: 85% completed LDCT scan 2 years: 82% completed scan	Not available

Table 4. Response, adherence and contamination rates *(Continued)*

		3 years: 80% completed scan	
Pastorino 2012	Not available	Baseline: 97% of annual group completed scan, 97% of biennial group completed scan 1 year: 97% of the annual group and 97% of the biennial group completed the scan 2 years: 98% of the annual group and 95% of the biennial group completed the scan 3 years: 97% of the annual group and 97% of the biennial group completed the scan 4 years: 96% of the annual group and 92% of the biennial group completed the scan 5 years: 79% of the annual group and 98% of the biennial group completed the scan 6 years: 54% of the annual group and 77% of the biennial group completed the scan	10 years post-randomisation: 21 of 1723 participants in the control arm had received a LDCT
Wille 2016	• 5861 people assessed for eligibility • 4104 people randomised to the trial (70% of people assessed)	Not available	After 5 years post-randomisation: 0 cases of contamination in the intervention arm; 3 cases in the control arm

CT: computed tomography; **CXR**: chest x-ray; **LDCT**: low-dose computed tomography

Table 5. Interval cancers and incidental findings

	Interval cancers	Incidental findings
Aberle 2011	Postbaseline LDCT: 18 lung cancers Post-1 year LDCT: 10 lung cancers	Baseline LDCT data from non-ACRIN centres (N = 17,309): 2625 cardiovascular abnormalities, 221 thyroid abnormalities, 419 adrenal abnormalities, 780 renal abnormalities, and 1064 hepatobiliary abnormalities
Becker 2020	Postbaseline LDCT: 1 lung cancer Post-1-year LDCT: 0 lung cancers Post-2-year LDCT: 2 lung cancers Post-3-year LDCT: 1 lung cancer	Not available

Table 5. Interval cancers and incidental findings *(Continued)*

	Post-4-year LDCT: 2 lung cancers	
Blanchon 2007	Not available	Baseline LDCT: 19 severe emphysema, 63 bronchiectasis, and 18 mediastinal findings Baseline CXR in control group: 5 severe emphysema, 2 bronchiectasis, and 6 mediastinal findings
De Koning 2020	After 3 rounds of LDCT screening: 35 interval lung cancers	Baseline LDCT data from one centre (N = 1929): 76 liver findings, 53 kidney findings, 9 thyroid findings, 2 mediastinal findings, 1 adrenal finding, 1 breast finding, 1 colon finding, and one perineural cyst
Field 2021	Not available	Baseline LDCT: 4 aortic dilatations, 5 severe aortic valva calcifications, 4 mediastinal masses, 6 mediastinal or hilar lymphadenopathy, 41 pneumonias, 5 bronchiectasis, 8 pleural thickening, 7 smoking related interstitial lung diseases, 9 severe emphysemas, 6 unspecified interstitial fibrosing lung disease, 2 nonspecific interstitial pneumonias, 12 usual interstitial pneumonias, 1 sarcoidosis, 2 oesophageal thickening or dilatation, 1 breast mass, 2 lobar collapse, 1 biliary dilatation, 3 adrenal masses, 1 liver cirrhosis, 1 hydronephrosis, 1 liver mass, 1 pancreatic cyst, 3 renal masses, 1 splenomegaly, and 1 thyroid mass
Gohagan 2005	1 year post-randomisation: 2 lung cancers in the LDCT group and 2 lung cancers in the control group	Not available
Infante 2015	Not available	Baseline LDCT: 1 lymphoma, 1 oesophageal carcinoma, 1 malignant mesothelioma, 1 colon cancer with liver metastasis, and 2 renal cancers with pulmonary metastasis Baseline CXR in the control group: 1 lymphoma
LaRocca 2002	Not available	Not available
Paci 2017	Overall 6 interval lung cancers reported during 4 years of screening	Not available
Pastorino 2012	• 4.4 years post-randomisation: 5 lung cancers reported in annual group and 5 in the biennial group • 6.5 years post-randomisation: 13 lung cancers reported in annual group and 10 in biennial group	Not available
Wille 2016	1 interval lung cancer reported in LDCT group during year 3	After 5 rounds of screening: 140 participants had 148 significant incidental findings (1 larynx, 3 thyroid, 9 gastroesophageal, 16 breast, 5 cardiac, 12 mediastinum, 28 aorta, 18 liver/gallbladder, 6 pancreas, 1 spleen, 2 intestines, 40 kidneys, 2 skin, 3 chest wall, and 2 vertebral column)

CXR: chest x-ray; **LDCT**: low-dose computed tomography

APPENDICES

Appendix 1. CENTRAL search strategy

1. MeSH descriptor: [Lung Neoplasms] explode all trees
2. "Bronchopulmonary carcino*" or "Cancer of Lung*" or "Cancer of the Lung*" or "Lung adenocarcimoma*" or "Lung Cancer*" or "Lung carcinoma*" or "Lung malignan*" or "Lung Neoplasm*" or "Lung Tumo*" or "Pulmonary adenocarcinoma*" or "Pulmonary Cancer*" or "pulmonary carcino*" or "pulmonary malignan*" or "Pulmonary Neoplasm*" or "Pulmonary tumo*"
3. MeSH descriptor: [Carcinoma, Non-Small-Cell Lung] explode all trees
4. "Nonsmall Cell Lung Cancer*" or "Non Small Cell Lung Cancer*" or "Nonsmall Cell Lung Carcinoma*" or "Non Small Cell Lung Carcinoma*" or NSCLC
5. MeSH descriptor: [Small Cell Lung Carcinoma] explode all trees
6. "Oat Cell Carcinoma*" or "Oat Cell Lung Cancer*" or SCLC or "Small Cell Lung Cancer*" or "Small Cell Lung Carcinoma*"
7. MeSH descriptor: [Pleural Neoplasms] explode all trees
8. mpm or "Pleural cancer*" or "pleural malignan*" or "pleural mesothelioma*" or "Pleural Neoplasm*" or "pleural tumo*"
9.#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
10. MeSH descriptor: [Tomography, X-Ray Computed] explode all trees
11. "CT Scan*" OR "Computed Tomography" OR "Computerized Tomography" OR "CT X Ray*" OR Tomodensitometry OR "CAT Scan" OR "Cine CT" OR "Electron Beam Tomography"
12. #10 OR #11
13. #9 AND #12

Appendix 2. MEDLINE search strategy

#21	**#10 AND #20**
#20	**#18 NOT #19**
#19	**animals [mh] NOT humans [mh]**
#18	**#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17**
#17	**trial [ti]**
#16	**ly [tiab]**
#15	**clinical trials as topic [mesh: noexp]**
#14	**placebo [tiab]**
#13	**randomised [tiab]**
#12	**controlled clinical trial [pt]**
#11	**randomised controlled trial [pt]**
#10	**#6 AND #9**
#9	**#7 OR #8**
#8	**CT Scan*[Title/Abstract] OR Computed Tomography[Title/Abstract] OR Computerized Tomography[Title/Abstract] OR CT X Ray*[Title/Abstract] OR Tomodensitometry[Title/Abstract] OR CAT Scan[Title/Abstract] OR Cine CT[Title/Abstract] OR Electron Beam Tomography[Title/Abstract]**
#7	**Tomography, X-Ray Computed[MeSH Terms]**
#6	**#1 OR #2 OR #3 OR #4 OR #5**

(Continued)

#5	**Pleural Neoplasms[MeSH Terms] OR mpm[Title/Abstract] OR Pleural cancer*[Title/Abstract] OR pleural malignan*[Title/Abstract] OR pleural mesothelioma*[Title/Abstract] OR Pleural Neoplasm*[Title/Abstract] OR pleural tumo*[Title/Abstract]**
#4	**Small Cell Lung Carcinoma[MeSH Terms] OR Oat Cell Carcinoma*[Title/Abstract] OR Oat Cell Lung Cancer*[Title/Abstract] OR SCLC[Title/Abstract] OR Small Cell Lung Cancer*[Title/Abstract] OR Small Cell Lung Carcinoma*[Title/Abstract]**
#3	**Search Carcinoma, Non-Small-Cell Lung[MeSH Terms] OR Nonsmall Cell Lung Cancer*[Title/Abstract] OR Non Small Cell Lung Cancer*[Title/Abstract] OR Nonsmall Cell Lung Carcinoma*[Title/Abstract] OR Non Small Cell Lung Carcinoma*[Title/Abstract] OR NSCLC [Title/Abstract]**
#2	**Bronchopulmonary carcino*[Title/Abstract] OR Cancer of Lung*[Title/Abstract] OR Cancer of the Lung*[Title/Abstract] OR Lung adenocarcimoma*[Title/Abstract] OR Lung Cancer*[Title/Abstract] OR Lung carcinoma*[Title/Abstract] OR Lung malignan*[Title/Abstract] OR Lung Neoplasm*[Title/Abstract] OR Lung Tumo*[Title/Abstract] OR Pulmonary adenocarcinoma*[Title/Abstract] OR Pulmonary Cancer*[Title/Abstract] OR pulmonary carcino*[Title/Abstract] OR pulmonary malignan*[Title/Abstract] OR Pulmonary Neoplasm*[Title/Abstract] OR Pulmonary tumo*[Title/Abstract]**
#1	**Lung Neoplasms[MeSH Terms]**

Appendix 3. Embase search strategy

#8	#5 AND #6 AND #7
#7	'crossover procedure'/exp OR 'double-blind procedure'/exp OR 'randomised controlled trial'/exp OR 'single-blind procedure'/exp OR random* OR factorial* OR crossover* OR (cross NEXT/1 over*) OR placebo* OR (doubl* NEAR/1 blind*) OR (singl* NEAR/1 blind*) OR assign* OR allocat* OR volunteer*
#6	'ct scan*':ti,ab OR 'computed tomography':ti,ab OR 'computerized tomography':ti,ab OR 'ct x ray*':ti,ab OR 'tomodensitometry':ti,ab OR 'cat scan':ti,ab OR 'cine ct':ti,ab OR 'electron beam tomography':ti,ab OR 'x-ray computed tomography'/exp
#5	#1 OR #2 OR #3 OR #4
#4	'pleura tumour'/exp OR 'mpm':ti,ab OR 'pleural cancer*':ti,ab OR 'pleural malignan*':ti,ab OR 'pleural mesothelioma*':ti,ab OR 'pleural neoplasm*':ti,ab OR 'pleural tumo*':ti,ab
#3	'small cell lung cancer'/exp OR 'oat cell carcinoma*':ti,ab OR 'oat cell lung cancer*':ti,ab OR 'sclc':ti,ab OR 'small cell lung cancer*':ti,ab OR 'small cell lung carcinoma*':ti,ab
#2	'non small cell lung cancer'/exp OR 'nonsmall cell lung cancer*':ti,ab OR 'non small cell lung cancer*':ti,ab OR 'nonsmall cell lung carcinoma*':ti,ab OR 'non small cell lung carcinoma*':ti,ab OR 'nsclc':ti,ab
#1	'bronchopulmonary carcino*':ti,ab OR 'cancer of lung*':ti,ab OR 'cancer of the lung*':ti,ab OR 'lung adenocarcimoma*':ti,ab OR 'lung cancer*':ti,ab OR 'lung carcinoma*':ti,ab OR 'lung malignan*':ti,ab OR 'lung neoplasm*':ti,ab OR 'lung tumo*':ti,ab OR 'pulmonary adenocarcinoma*':ti,ab

(Continued)

OR 'pulmonary cancer*':ti,ab OR 'pulmonary carcino*':ti,ab OR 'pulmonary malignan*':ti,ab OR 'pulmonary neoplasm*':ti,ab OR 'pulmonary tumo*:ti,ab' OR 'lung tumor'/exp

HISTORY

Protocol first published: Issue 12, 2020

CONTRIBUTIONS OF AUTHORS

Design of the protocol: AB, RM, CM, DM, KMF, HMM, LBI, RManser

Selection of studies: AB, CM, DM, RManser

Data extraction and management: AB, RM, DM, RManser

Assessment of risk of bias: AB, RM, DM, RManser

Dealing with missing data: DM

Data analysis: AB, RM

Manuscript preparation: AB, RM, CM, DM, KMF, HMM, LBI, RManser

DECLARATIONS OF INTEREST

Asha Bonney has a Postgraduate Scholarship from the Australian National Health and Medical Research Council.

Reem Malouf: none known

Corynne Marchal: none known

David Manners has received speaking honoraria from Astra Zeneca and research grant funding from Curtin Medical School, Curtin University.

Kwun M Fong: Co-investigator on the International Lung Screening Trial. This is an international, multicentre, investigator initiated study, funded in Australia by a National Health and Medical Research Grant. The study is an observational cohort study examining low-dose screening for lung cancer in high-risk former and current smokers. KF also undertook the QLCSS lung cancer screening trial, a pilot one-armed study which is not eligible as it is not a RCT - Queensland Smart State Grant.
Chair of the Lung Cancer Consultative Group for NGO Lung Foundation Australia (no payment).
KF declares occasional speaking on lung cancer at conferences and meetings where industry may be the organiser or a sponsor.
KF has an Australian Medical Research Future Fund Fellowship. KF received in-kind support with software licences for MeVis Veolity Computer Aided Diagnosis for the ILST clinical trial. KF is a reviewer for UpToDate (not related to CT screening). KF is Editor for the Cochrane Lung Cancer Group.

Henry M Marshall is an investigator on the International Lung Screen Trial. He has received honoraria to speak on the subjects of smoking cessation, lung cancer screening and COPD.

Louis B Irving: none known

Renée Manser: none known. Co-editor, Cochrane Lung Cancer Review Group
Co-investigator on the International Lung Screening Trial. This is an international, multicentre, investigator initiated trial, funded in Australia by a National Health and Medical Research Grant. The study is an observational cohort study examining low-dose screening for lung cancer in high-risk former and current smokers.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- Institut National du Cancer (INCa), France
  - INCa n° 2017-186

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- The title has been changed to better reflect the purpose of the review.
- Analysis: during the review process we decided to look at all outcomes using both random-effects and fixed-effect models to see if there was any difference given the significance of the variables. We presented both random- and fixed-effects analyses only when there was a notable difference. When results were similar, we presented only the random-effects analysis.
- Subgroup analysis: we added the subgroup 'control arm intervention'.
- In the summary of findings table:
  - we removed smoking outcomes and recall rates due to limited data. Instead, we included an additional harm outcome (any death postsurgery);
  - we replaced lung cancer incidence with overdiagnosis;
  - we specifically chose to present anxiety data as an example of psychosocial consequences of screening, as it had the most robust data available.

NOTES

Some parts of the methods sections come from a standard template drafted by the Cochrane Lung Cancer Group.

INDEX TERMS

Medical Subject Headings (MeSH)

Bias; *Early Detection of Cancer [methods]; *Lung Neoplasms [diagnostic imaging] [mortality]; Randomized Controlled Trials as Topic; Tomography, X-Ray Computed [methods]

MeSH check words

Adult; Female; Humans; Male