original reports

Benefits and Harms of Lung Cancer Screening by Chest Computed Tomography: A Systematic Review and Meta-Analysis

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abstract

PURPOSE This meta-analysis aims to combine and analyze randomized clinical trials comparing computed tomography lung screening (CTLS) versus either no screening (NS) or chest x-ray (CXR) in subjects with cigarette smoking history, to provide a precise and reliable estimation of the benefits and harms associated with CTLS.

MATERIALS AND METHODS Data from all published randomized trials comparing CTLS versus either NS or CXR in a highly tobacco-exposed population were collected, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Subgroup analyses by comparator (NS or CXR) were performed. Pooled risk ratio (RR) and relative 95% CIs were calculated for dichotomous outcomes. The certainty of the evidence was assessed using the GRADE approach.

RESULTS Nine eligible trials (88,497 patients) were included. Pooled analysis showed that CTLS is associated with: a significant reduction of lung cancer–related mortality (overall RR, 0.87; 95% CI, 0.78 to 0.98; NS RR, 0.80; 95% CI, 0.69 to 0.92); a significant increase of early-stage tumors diagnosis (overall RR, 2.84; 95% CI 1.76 to 4.58; NS RR, 3.33; 95% CI, 2.27 to 4.89; CXR RR, 1.52; 95% CI, 1.04 to 2.23); a significant decrease of late-stage tumors diagnosis (overall RR, 0.75; 95% CI, 0.68 to 0.83; NS RR, 0.67; 95% CI, 0.56 to 0.80); a significant increase of resectability rate (NS RR, 2.57; 95% CI, 1.76 to 3.74); a nonsignificant reduction of all-cause mortality (overall RR, 0.99; 95% CI, 0.94 to 1.05); and a significant increase of overdiagnosis rate (NS, 38%; 95% CI, 14 to 63). The analysis of lung cancer–related mortality by sex revealed nonsignificant differences between men and women (P = .21; I-squared = 33.6%).

CONCLUSION Despite there still being uncertainty about overdiagnosis estimate, this meta-analysis suggested that the CTLS benefits outweigh harms, in subjects with cigarette smoking history, ultimately supporting the systematic implementation of lung cancer screening worldwide.

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INTRODUCTION

Updated epidemiologic data described a continuous reduction of lung cancer incidence within the US population, while it still remains the main cause of cancer mortality, with an estimated 72,500 new deaths in men and 63,220 in women for 2020.[1] Similarly, in Europe, the highest 2020 predicted tumor mortality was ascribed to lung cancer.[2] Since the high mortality rate observed in patients with lung cancer is mainly attributable to delayed diagnosis, implementing lung cancer screening by computed tomography (CT) is emerging as a valid strategy to increase curative approaches and definitively impact on patients' survival. In 2011, the National Lung Cancer Screening Trial (NLST)[3] demonstrated that the use of annual computed tomography lung screening (CTLS) produced a significant 20% reduction of lung cancer deaths as compared to the chest x-ray (CXR) in a selected US population highly exposed to tobacco, leading to the recommendation of CTLS by the US Preventive Services Task Force, for adults aging between 55 and 80 years with relevant smoking history.[4] Afterward, several randomized clinical trials[5-14] compared CTLS versus usual care in high-risk smoking population across different European countries. Despite similar eligibility criteria, study design, and follow-up duration, the majority of these studies failed to show a significant reduction of lung cancer–related mortality in subjects undergoing CTLS, likely because of the low number of included subjects and limited follow-up. Recently, the final results of the largest European randomized NELSON trial demonstrated a significant survival benefit associated with the annual CTLS in a tobacco-exposed population. However, concerns about the rate of overdiagnosis and economic impact along with uncertain risk-benefit ratio remain still major

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

This meta-analysis provides an updated estimation of the benefits and harms associated with computed tomography lung screening (CTLS) in subjects with cigarette smoking history, which may serve as scientific support for evidence-based guidelines.

Knowledge Generated

CTLS was associated with a significant 20% reduction of lung cancer–related mortality, without differences between men and women. A significant increase in early-stage tumors diagnosis and resectability rate along with a decrease in late-stage tumors diagnosis was observed. A significant increase of the overdiagnosis rate was reported too.

Relevance

Findings from this work suggested that the potential benefits associated with CTLS outweigh harms, in subjects with cigarette smoking history, ultimately supporting the systematic implementation of lung cancer screening worldwide.

barriers to the implementation of screening services by the European governments. Following the publication of the NELSON study, as the panel of specialists responsible for drafting the Italian Association of Medical Oncology lung cancer guidelines,[15,16] we decided to include a clinical question specifically dedicated to the use of CTLS as the secondary prevention tool in the high-risk smoking population. Indeed, in Italy, as well as in other countries, there is an urgent need of evidence-based recommendations for a safe and effective implementation of lung cancer screening in the real-world scenario. This work aims to combine and simultaneously analyze all the available randomized clinical trials comparing CTLS versus either no screening (NS) or CXR in tobacco-exposed population, to provide a precise and reliable estimation of the benefits and harms associated with CTLS, which may serve as scientific support for regulatory decision making.

MATERIALS AND METHODS

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[17] The systematic review was registered on the International prospective register of systematic reviews (PROSPERO): CRD42018105409.

Inclusion Criteria

We included randomized controlled trials comparing CTLS with either NS or CXR in a high-risk population with a cigarette smoking history of at least 15 pack-years, including former smokers who had quit within the previous 15 years.

The primary outcome was lung cancer–related mortality. Secondary outcomes assessed were any cause-related mortality, resectability rate, diagnosis of early-stage tumors, diagnosis of late-stage tumors, and overdiagnosis.

In detail, resectability rate was defined as the ratio of incidence of participants undergoing a surgery procedure related to screening findings in each study arm; diagnosis of early-stage tumors was defined as the ratio of the incidence of stage I-II cancers detected in each study arm; diagnosis of late-stage tumors was defined as the ratio of the incidence of stage IV cancers detected in each study arm; overdiagnosis was defined as the ratio between the difference of cumulative cancer incidence in the screened versus the control population, and the cumulative number of screen-detected cancers (defined as all cancers detected by screening in the population offered screening during the active phase).

Identification of Eligible Trials

Cochrane Database of Systematic Reviews (CENTRAL), Embase, MEDLINE, and ClinicalTrial.gov were searched for eligible studies. A literature search was performed using free text and Mesh terms from inception up to February 13, 2020, without language restriction.

Data Collection and Analyses

Two authors independently screened articles retrieved from title and abstracts. Full text of potentially relevant studies was independently retrieved and assessed for final inclusion by two different authors and any disagreement discussed with a third author. Two review authors independently extracted the following data: number and characteristics of participants (mean age, sex, smoking status, cigarettes smoked per day or pack-years, and years since smoking cessation); nodule evaluation method and screening positivity criteria; length of follow-up; type of interventions and control arm; and country where the study was conducted.

Two authors independently assessed risk of bias according to the following criteria suggested by the Cochrane Handbook for Systematic Reviews of Interventions[18]: sequence generation and allocation concealment (selection bias), blinding of participants and providers (performance bias), blinding of outcome assessors (detection bias), incomplete outcome data (attrition bias), and selective outcome reporting (reporting bias).

We analyzed dichotomous outcomes by calculating the risk ratio (RR) for each trial, and the uncertainty in each result was expressed with a 95% CI.

When the number of events and the total number of participants enrolled were not available per arm, but the primary studies reported relative effects and their 95% CIs, we pooled data with the generic inverse of variance methods and expressed results as effect size and its 95% CIs. We interpreted effect size values with the classification proposed by Cohen[19] where an effect size of 0.2 means a small effect, 0.5 means a medium effect, and 0.8 means a large effect.

For overdiagnosis, we used the inverse of variance method (SE was calculated using the error propagation formula).

As we supposed a certain degree of heterogeneity among studies, because of screening program and usual care in the control arm, risk of bias, and other factors that may have affected direction and magnitude of treatment effect, we pooled data using the random effect model for each outcome.

Statistical heterogeneity among studies was assessed by the Cochrane Q-test, setting a significant threshold of alpha = .1, whereas inconsistency among studies was quantified by the I-squared statistic[18]; an I-squared > 70% was judged as indicative of significant heterogeneity.

The results are depicted as conventional meta-analysis forest plots. RevMan 5.3 was used.[20]

We decided to visually inspect the funnel plots (plots of the effect estimate from each study against the sample size or effect SE) to indicate possible publication bias if there were at least 10 studies included in the meta-analysis.

Subgroup Analysis

We analyzed the effect of CTLS in subgroups based on both comparator arm (eg, NS or CXR) for all outcomes, and sex (male or female) for the primary outcome of lung cancer-related mortality. As regards sex-based analysis, we reported the subgroups pooled estimates only.

Grading of Evidence

We assessed the overall certainty of the evidence for primary and secondary outcomes using the five GRADE domains (study limitations, consistency of effect, imprecision, indirectness, and publication bias) according to the GRADE approach.[21]

The existing evidence was summarized in a Summary of Findings table that provides key information about the magnitudes of relative and absolute effects of the interventions, the amount, and the certainty of available evidence.[22]

RESULTS

The database searches retrieved 137 records after duplicates were removed. Sixteen studies were judged as potentially relevant. Two articles were excluded because they were not randomized controlled trials and five articles because they did not include either population (n = 3) or intervention (n = 2) of interest. Six randomized controlled trials comparing CTLS versus NS[6,8,10,11,13,14] and three comparing CTLS versus CXR[3,23-25] were finally included (Appendix Fig A1, online only). These trials enrolled a total of 88,497 participants, with sample size ranging from 621 in the DESPICAN to 53,452 in the NLST studies.[24,3] In detail, a total of 31,106 and 57,391 participants were included in CTLS versus NS and CTLS versus CXR randomized trials, respectively.

Most of the participants were male, with female percentages ranging from 29.5% in the DESPICAN[24] to 44.8% in the DLCST trials[8]; no females were included within the Italian DANTE study.[6] In almost all included trials, baseline characteristics were well balanced between the two studies' groups. Three studies were conducted in Italy,[6,10,13] two in United States,[3,23] and one each in the Netherlands,[14] Germany,[11] Denmark,[8] and France.[24] Table 1 summarizes the main characteristics of each trial.

Effects of Computed Tomography Screening

Lung cancer–related mortality. We found a significant reduction in favor of CTLS both in the overall population (RR, 0.87; 95% CI, 0.78 to 0.98; $I^2 = 24\%$, eight studies, 87,876 participants) and in the NS group (RR, 0.80; 95% CI, 0.69 to 0.92; $I^2 = 0\%$, six studies, 31,106 participants). No significant differences were observed in the CXR group (RR, 0.95; 95% CI, 0.82 to 1.10; $I^2 = 11\%$, two studies, 56,770 participants; Fig 1A).

The anticipated absolute effect showed that five fewer per 1,000 participants (95% CI, 8 fewer to 2 fewer) would experience a lung cancer–related death if screened, when compared with NS, and two fewer per 1,000 participants (95% CI, 8 fewer to 4 more) when compared with CXR. Quality of evidence was high for the primary outcome (Table 2).

All-cause mortality. Overall, we found a nonsignificant reduction in favor of CTLS (RR, 0.99; 95% CI, 0.94 to 1.05; $I^2 = 27\%$, eight studies, 87,876 participants). The results were similar in both NS (RR, 0.98; 95% CI, 0.90 to 1.07; $I^2 = 27\%$, six studies, 31,106 participants) and CXR (RR, 1.04; 95% CI, 0.87 to 1.26; $I^2 = 63\%$, two studies, 56,770 participants) subgroups (Fig 1B).

The anticipated absolute effect shows that two fewer per 1,000 participants (95% CI, 10 fewer to 7 more) would experience an all-cause death if screened, when compared with NS, and eight more per 1,000 participants (95% CI, 25 fewer to 50 more) when compared with CXR (Table 2).

Diagnosis of early-stage tumors. Overall, we found a significant increase in favor of the CTLS (RR, 2.42; 95% CI, 1.71 to 3.44; $I^2 = 81\%$, nine studies, 88,497 participants; Fig 2A).

TABLE 1. Characteristics of the Randomized Studies Included in the Meta-Analysis

Trial (country)	Population	CT Interval (months/round)	Nodule Evaluation (positivity criteria)	Smoking History	Comparison Intervention	FU (years)	Participation Rate (%)
NLST (United States)[3]	N = 53,454 Men and women 55-75 years of age, current (48%) or former smokers of at least 30 pack-years who had quit < 15 years before Female: 41%	n = 26,722 CTLS (12/3)	CT scan: > 4-mm diameter	Pack-years: mean: 56.04 Cessation: NR	n = 26,732 Annual CXR	Median: 6.5	95
DANTE (Italy)[6]	N = 2,811 Men 60-74 years of age, current (1,395) or former smokers of at least 20 pack-years who had quit < 10 years before Female: not included	n = 1,403 CTLS (12/5)	CT scan: > 10-mm diameter	Pack-years: mean: 47.3 (SE 0.6) Cessation: NR	n = 1,408 Usual care	Median: 8.35	87.2
DLCST (Denmark)[8]	Men and women 50-70 years of age, current (3,124) and former smokers of at least 20 pack-years (980) who quit < 10 years before Female: 44.8%	n = 2,052 CTLS (12/5)	CT scan: size and growth as mean diameter: > 5-mm diameter All growing nodules[a]	Cigarettes/day: < 10: 1.37% 10-20: 15.47% 21-30: 8.52% > 40: 3.68% Cessation: < 5 to > 10 years	n = 2,052 Usual care	10	95.5
ITALUNG (Italy)[10]	N = 3,226 Men and women 55-69 years of age, current (1,128) and former smokers of at least 20 pack-years who quit < 10 years before Female: 35.1%	n = 1,613 CTLS (12/4)	CT scan: size and growth as mean diameter: > 5-mm diameter All growing nodules[b]	Pack-years: 20-30: 26.23% 30-50: 51.78% > 50: 21.99% Cessation: NR	n = 1,593 Usual care	Median: 9.3	81
LUSI (Germany)[11]	N = 4,052 Men and women 50-69 years of age, current (2,507) and former smokers with ≥ 25 years of smoking ≥ 15 cigarettes a day or 30 years of smoking ≥ 10 cigarettes per day Female: 35.29%	n = 2,029 CTLS (12/5)	CT scan: > 5-mm diameter	Pack-years: NR Cessation: < 10 years	n = 2,023 Usual care	Mean: 8.8	> 90
MILD (Italy)[13]	N = 4,099 Men and women 49-75 years of age, current (3,175) or former smokers ≥ 20 pack-years Female: 33.74%	n = 2,376 CTLS (12 or 24/6 or 3)	CT scan: nodule volume > 60 mm^3	Pack-years: < 30: 30.1% ≥ 30: 75.5% Cessation: < 10 years	n = 1,723 Usual care	10	96.1
NELSON (Netherlands)[14]	N = 13,195 Men 50-74 years of age, current (7,254) or former smokers (who had quit ≤ 10 years ago) who had smoked > 15 cigarettes a day for > 25 years or > 10 cigarettes a day for > 30 years Female: NR	n = 6,589 CTLS (12 or 24 or 30/4)	CT scan: nodule volume > 50 mm^3	Cigarettes/day: ≤ 10: 0.3% 11-15: 22.0% 16-20: 28.2% 21-25: 26.6% 26-30: 10.5% 31-40: 0.1% > 40: 0.05% Cessation: < 1 to > 10 years	n = 6,612 Usual care	10	85.8

(continued on following page)

TABLE 1. Characteristics of the Randomized Studies Included in the Meta-Analysis (continued)

Trial (country)	Population	CT Interval (months/round)	Nodule Evaluation (positivity criteria)	Smoking History	Comparison Intervention	FU (years)	Participation Rate (%)
LSS[23]	N = 3,318 Men and women 55-74 years of age, current (58%) or former smokers of at least 30 pack-years who had quit < 10 years before Female: 41%	n = 1,660 CTLS (12/1)	CT scan: > 5-mm diameter	Pack-years: mean: 54 Cessation: NR	n = 1,658 Annual CXR	NR	86
DEPISCAN[24]	N = 765 Men and women 50-75 years of age, current (64%) or former smokers of at least 15 pack-years who had quit < 15 years before Female: 30%	n = 385 CTLS (12/3)	CT scan: size as mean diameter > 5-mm diameter	Cigarettes/day: median: 1-1.5 Cessation: NR	n = 380 Annual CXR	NR	NR

Abbreviations: CT, computed tomography; CTLS, computed tomography lung cancer screening; CXR, chest x-ray; FU, follow-up; NR, not reported.

[a]Growth defined as increase in volume of at least 25%.

[b]Growth defined as 1-mm increase of a solid or subsolid nodule.

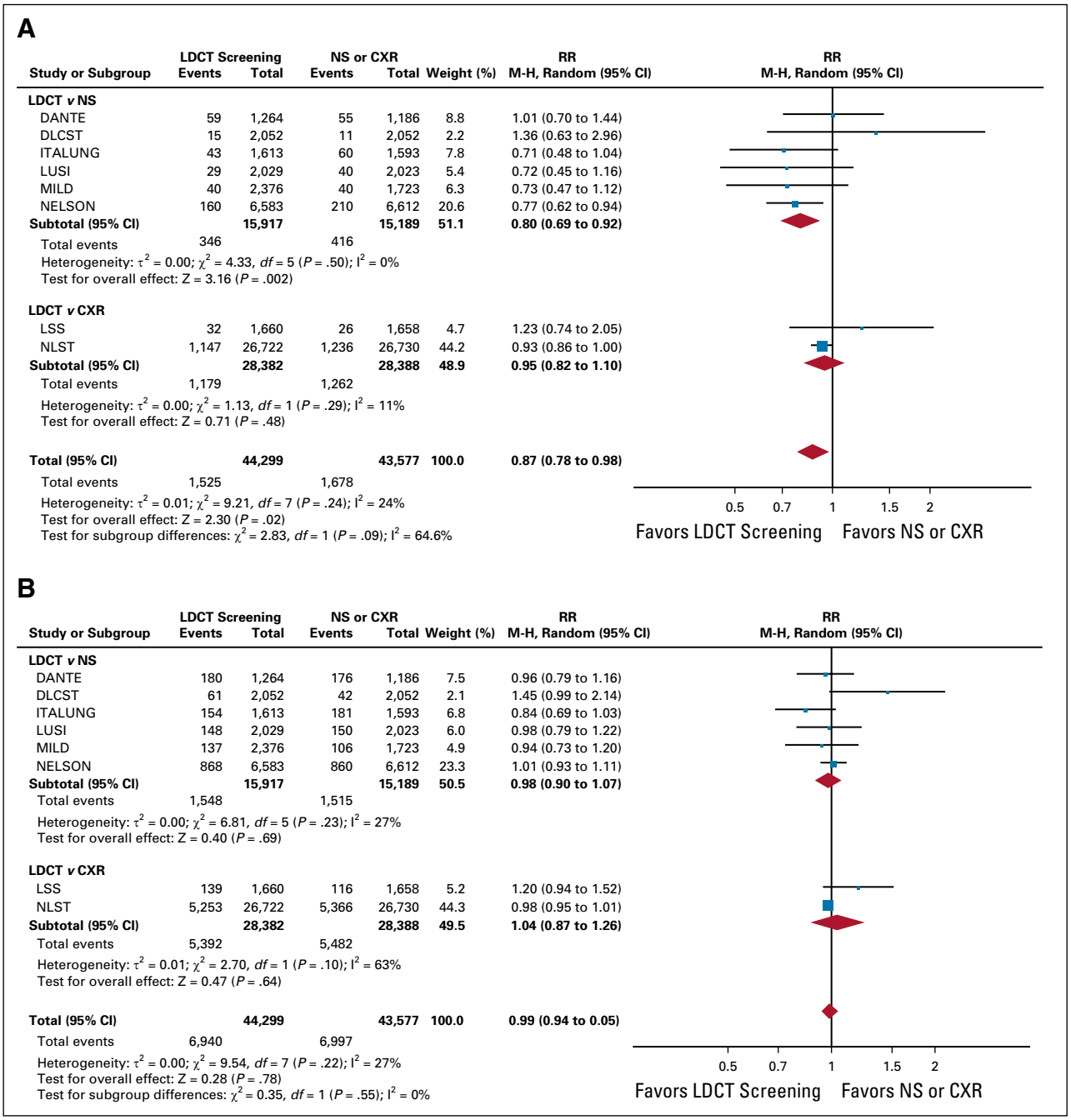

FIG 1. Forest plot showing RR for (A) lung cancer–related mortality and (B) all cause-related mortality in subjects undergoing computed tomography lung screening versus clinical observation or CXR. CXR, chest x-ray; LDCT, low-dose computed tomography; M-H, Mantel-Haenszel; NS, no screening; RR, risk ratio.

A larger increase was shown for CTLS versus NS (RR, 2.73; 95% CI, 1.91 to 3.90; I^2 = 63%, six studies, 31,106 participants) rather than for CTLS versus CXR (RR, 1.52; 95% CI, 1.04 to 2.23; I^2 = 24%, three studies, 57,391 participants; Fig 2A).

The anticipated absolute effect showed that 16 more per 1,000 participants (95% CI, 9 more to 27 more) would experience the diagnosis of an early-stage tumor when compared with NS and 11 more per 1,000 participants (95% CI, 1 more to 26 more) when compared with CXR (Table 2).

Diagnosis of late-stage tumors. Overall, we found a significant decrease in favor of the CTLS (RR, 0.75; 95% CI, 0.68 to 0.83; I^2 = 0%, nine studies, 88,641 participants; Fig 2B).

A larger decrease was shown for CTLS versus NS (RR, 0.67; 95% CI, 0.56 to 0.80; I^2 = 0%, six studies, 31,106 participants), whereas no significant differences were observed

TABLE 2. Summary of Pooled Relative and Absolute Effects and Quality of Evidence for Each Study Outcome

Outcomes	No. of Participants (studies) Follow-Up	Certainty of Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects	
				Risk With No-CTLS or CXR	Risk Difference With CTLS
Lung cancer–related mortality (overall) follow-up: range 3-12.3 years	87,876 (8 RCTs)	⨁⨁⨁⨁ High	RR 0.87 (0.78 to 0.98)	39 per 1.000	5 fewer per 1.000 (8 to 1 fewer)
Lung cancer–related mortality (CTLS *v* no CTLS) follow-up: range 3-8.35 years	31,106 (6 RCTs)	⨁⨁⨁⨁ High	RR 0.80 (0.69 to 0.92)	27 per 1.000	5 fewer per 1.000 (8 to 2 fewer)
Lung cancer–related mortality (CTLS *v* CXR) follow-up: 12.3 years	56,770 (1 RCT)	⨁⨁⨁⨁ High	RR 0.95 (0.86 to 1.00)	44 per 1.000	2 fewer per 1.000 (8 fewer to 4 more)
All-cause mortality (overall) follow-up: range 3-12.3 years	87,876 (8 RCTs)	⨁⨁⨁◯ Moderate[a]	RR 0.99 (0.94 to 1.05)	161 per 1.000	2 fewer per 1.000 (10 fewer to 8 more)
All-cause mortality (CTLS *v* no CTLS)	31,106 (6 RCTs)	⨁⨁⨁◯ Moderate[a]	RR 0.98 (0.90 to 1.07)	100 per 1.000	2 fewer per 1.000 (10 fewer to 7 more)
All-cause mortality (CTLS *v* CXR)	56,770 (2 RCTs)	⨁⨁⨁◯ Moderate[a]	RR 1.04 (0.87 to 1.26)	193 per 1.000	8 more per 1.000 (25 fewer to 50 more)
Early-stage tumor diagnosis (overall) follow-up: range 3-12.3 years	88,497 (9 RCTs)	⨁⨁⨁◯ Moderate[b]	RR 2.42 (1.71 to 3.44)	17 per 1.000	25 more per 1.000 (12 to 42 more)
Early-stage tumor diagnosis (CTLS *v* no CTLS) follow-up: range 3-8.35 years	31,106 (6 RCTs)	⨁⨁⨁◯ Moderate[b]	RR 2.73 (1.91 to 3.90)	9 per 1.000	16 more per 1.000 (9 to 27 more)
Early-stage tumor diagnosis (CTLS *v* CXR) follow-up: range 3-12.3 years	57,391 (3 RCTs)	⨁⨁⨁◯ Moderate[b]	RR 1.52 (1.04 to 2.23)	21 per 1.000	11 more per 1.000 (1 to 26 more)
Late-stage tumor diagnosis (overall) follow-up: range 3-12.3 years	8,641 (9 RCTs)	⨁⨁⨁◯ Moderate[b]	RR 0.75 (0.68 to 0.83)	20 per 1.000	5 fewer per 1.000 (6 to 3 fewer)
Late-stage tumor diagnosis (CTLS *v* no CTLS) follow-up: range 3-8.5 years	31,106 (6 RCTs)	⨁⨁⨁◯ Moderate[b]	RR 0.67 (0.56 to 0.80)	18 per 1.000	6 fewer per 1.000 (8 to 4 fewer)
Late-stage tumor diagnosis (CTLS *v* no CTLS) follow-up: range 3-12.3 years	57,535 (3 RCTs)	⨁⨁⨁◯ Moderate[b]	RR 1.21 (0.38 to 3.89)	21 per 1.000	4 fewer per 1.000 (16 fewer to 60 more)
Resectability rate (CTLS *v* no CTLS) follow-up: range 3-8.35 years	13,859 (4 RCTs)	⨁⨁⨁◯ Moderate[c]	RR 2.57 (1.76 to 3.74)	11 per 1.000	18 more per 1.000 (9 to 31 more)
Overdiagnosis rate (overall) follow-up: range 3-12.3 months	82,108 (6 RCTs)	⨁⨁◯◯ Low[b,d]	—	Mean 0	0.30 higher (0.06 to 0.55 higher)
Overdiagnosis rate (CTLS *v* no CTLS) follow-up: range 3-5 years	28,656 (5 RCTs)	⨁⨁◯◯ Low[b,d]	—	Mean 0	0.38 higher (0.14 to 0.63 higher)
Overdiagnosis rate (CTLS *v* CXR)	53,452 (1 RCT)	⨁⨁⨁◯ Moderate[b]	—	Mean 0	0.04 higher (0.1 lower to 0.18 higher)

NOTE. The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

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.

Abbreviations: CTLS, computed tomography lung cancer screening; CXR, chest x-ray; RCT, randomized clinical trial; RR, risk ratio.

[a]Certainty of evidence was downgraded by one level because of imprecision. Optimal information size not reached for screening studies.

[b]Certainty of evidence was downgraded by one level for high risk of performance and detection bias.

[c]Certainty of evidence was downgraded by one level for imprecision because of large confidence intervals.

[d]Certainty of evidence was downgraded by one level for inconsistency among studies.

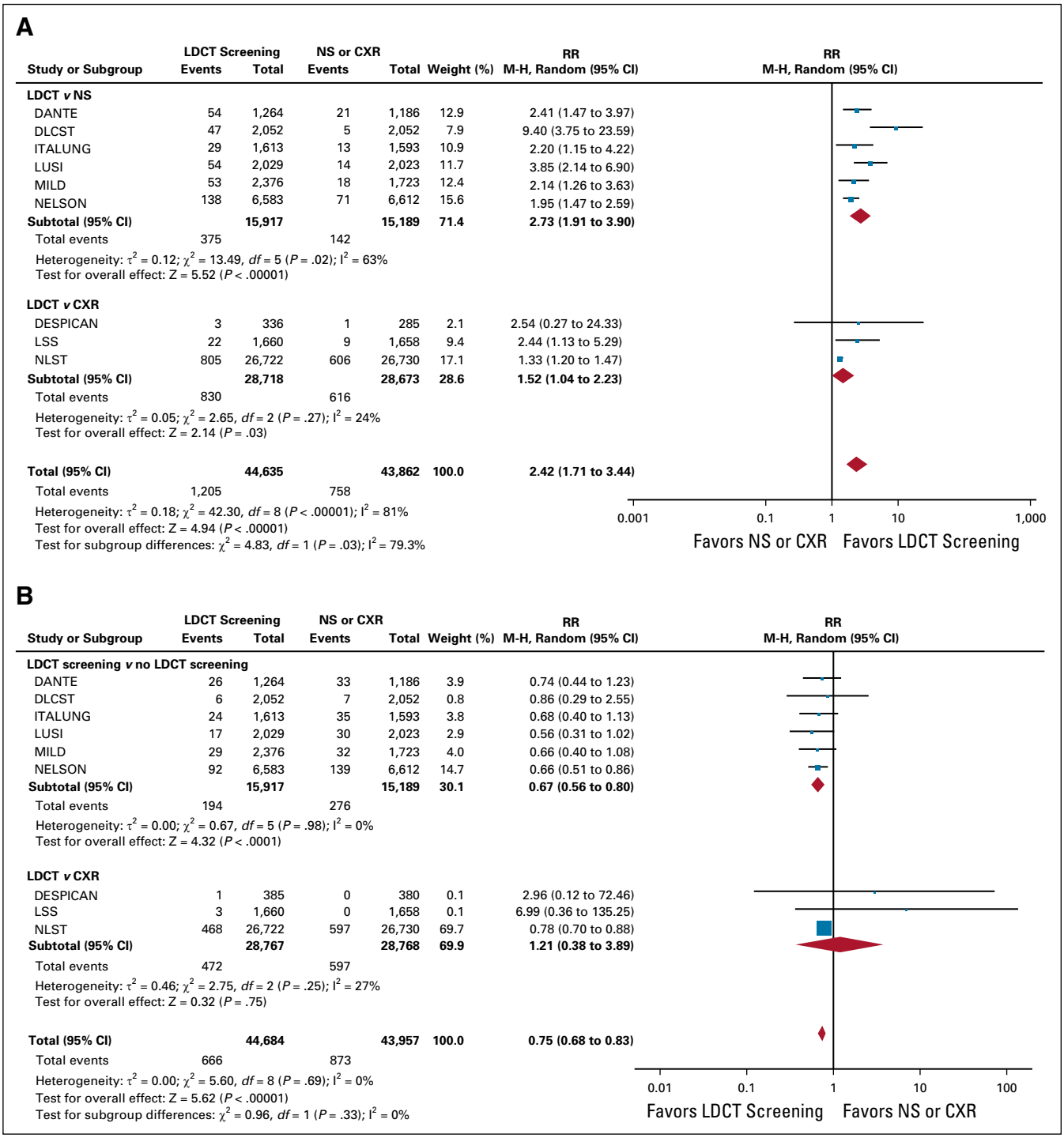

FIG 2. Forest plot showing RR for (A) early-stage tumor diagnosis rate and (B) late-stage tumor diagnosis rate in subjects undergoing computed tomography lung screening versus clinical observation or CXR. CXR, chest x-ray; LDCT, low-dose computed tomography; M-H, Mantel-Haenszel; NS, no screening; RR, risk ratio.

for CTLS versus CXR (RR, 1.21; 95% CI, 0.38 to 3.89; I^2 = 27%, three studies, 57,535 participants; Fig 2B).

The anticipated absolute effect showed that 6 fewer per 1,000 participants (95% CI, 8 fewer to 4 fewer) would experience the diagnosis of a late-stage tumor when compared with NS and four more per 1,000 participants (95% CI, 13 fewer to 60 more) when compared with CXR (Table 2).

Resectability rate. We found a significant increase with CTLS versus NS (RR, 2.57; 95% CI, 1.76 to 3.74; I^2 = 38%, four studies, 13,859 participants; Appendix Fig A2, online only).

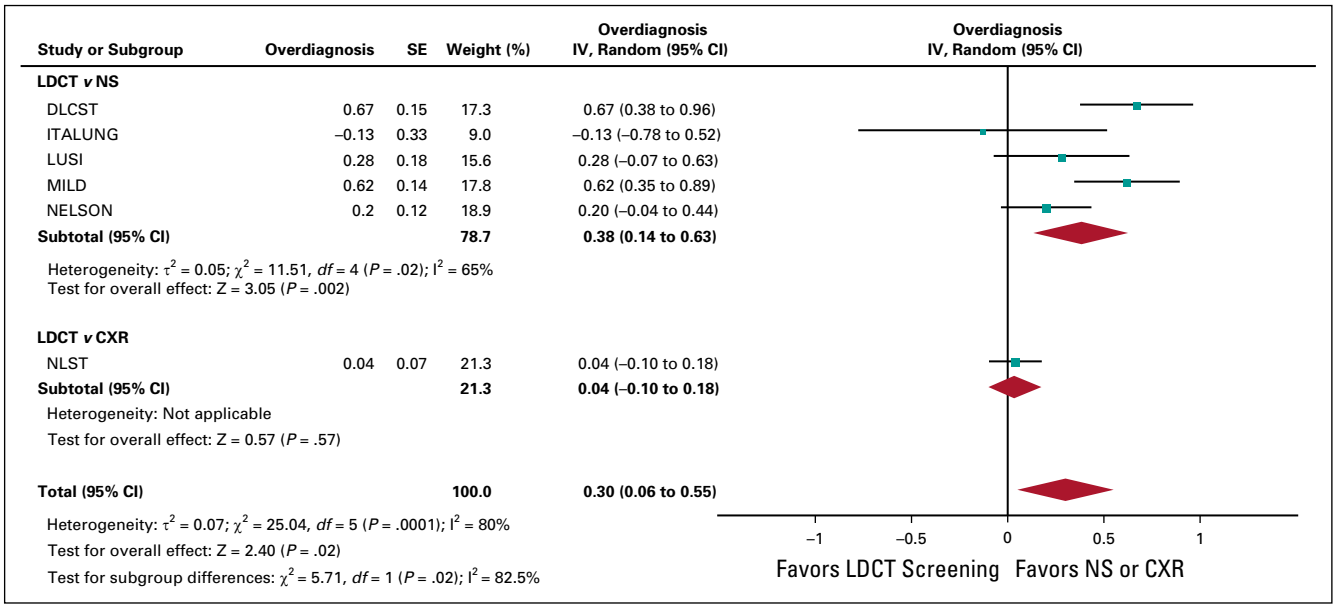

FIG 3. Forest plot showing percentage of overdiagnosis in subjects undergoing computed tomography lung screening versus clinical observation or CXR. CXR, chest x-ray; IV, inverse variance; LDCT, low-dose computed tomography; NS, no screening.

The anticipated absolute effect shows that 18 more per 1,000 participants (95% CI, 9 more to 31 more) would experience a resection for lung cancer when compared with NS (Table 2).

Overdiagnosis. We found a significant increase with CTLS in the overall population (30%; [95% CI, 6 to 55]; $I^2 = 80\%$, six studies, 82,108 participants), as well as in CTLS versus NS group (38%; [95% CI, 14 to 63]; $I^2 = 65\%$, five studies, 28,656 participants). No difference was found for CTLS versus CXR comparison (4%; [95% CI, −10 to 18; one study, 55,386 participants; Fig 3).

The certainty of the evidence was moderate for all the study secondary outcomes and low for overdiagnosis (Table 2).

We did not evaluate publication bias by visual inspection of the funnel plot because only six trials for CTLS versus NS, and only three versus CXR, were found.

Subgroup Analysis

The subgroup analysis of lung cancer–related mortality by sex revealed a nonsignificant difference between men and women ($P = .21$; I-squared = 33.6%; Fig 4).

For the male participants' subgroup, we found a small effect (effect size [ES] = −0.17; 95% CI, −0.33 to −0.01; $I^2 = 0\%$; four studies) when CTLS was compared with NS; we found a nonstatistically significant effect (ES = −0.02; 95% CI, −0.08 to 0.04; one study) when CTLS was compared with CXR.

For the female participants' subgroup, we found a nonstatistically significant effect when CTLS was compared with both NS (ES = −0.32; 95% CI, −0.97 to 0.32; $I^2 = 62\%$; three studies) and CXR (ES = −0.08; 95% CI, −0.16 to 0; one study).

Risk of Bias in Included Studies

Five studies[8,10,11,14,23] were judged at low risk of selection bias because both the methods for random sequence generation and allocation concealment were appropriate. The remaining four studies[3,6,13,24] did not provide information about random sequence generation and concealment of allocation and were therefore judged at unclear risk for selection bias. All studies except one[8] were open-label and were judged at high risk for both performance and detection bias. One study[8] was single-blind and was judged at high risk of performance only. Six studies were judged at low risk of attrition bias.[3,8,10,11,14,23] Two studies[6,13] did not provide information about subjects dropped out from each group. DEPISCAN study was judged at high risk of attrition bias for unbalanced withdrawn in the two study arms.[24] The study protocol was available for six studies[3,6,8,10,13,23] and the outcomes reported in the final publication coincided with the outcomes listed in the protocol; for the remaining studies,[11,14,24] the protocol was not available and they were judged at unclear risk of selective outcome reporting (Appendix Fig A3, online only).

DISCUSSION

In *JAMA Internal Medicine*, Clark et al[26] pointed out a significant imbalance for the presentation of lung cancer screening benefits and harms in a large fraction of US screening program websites and highlighted the lack of guideline-driven recommendations for shared decision-making in this setting. This meta-analysis provides an updated and reliable estimation of both desirable and undesirable effects related to CTLS in subjects with cigarette smoking history, which may serve as scientific support

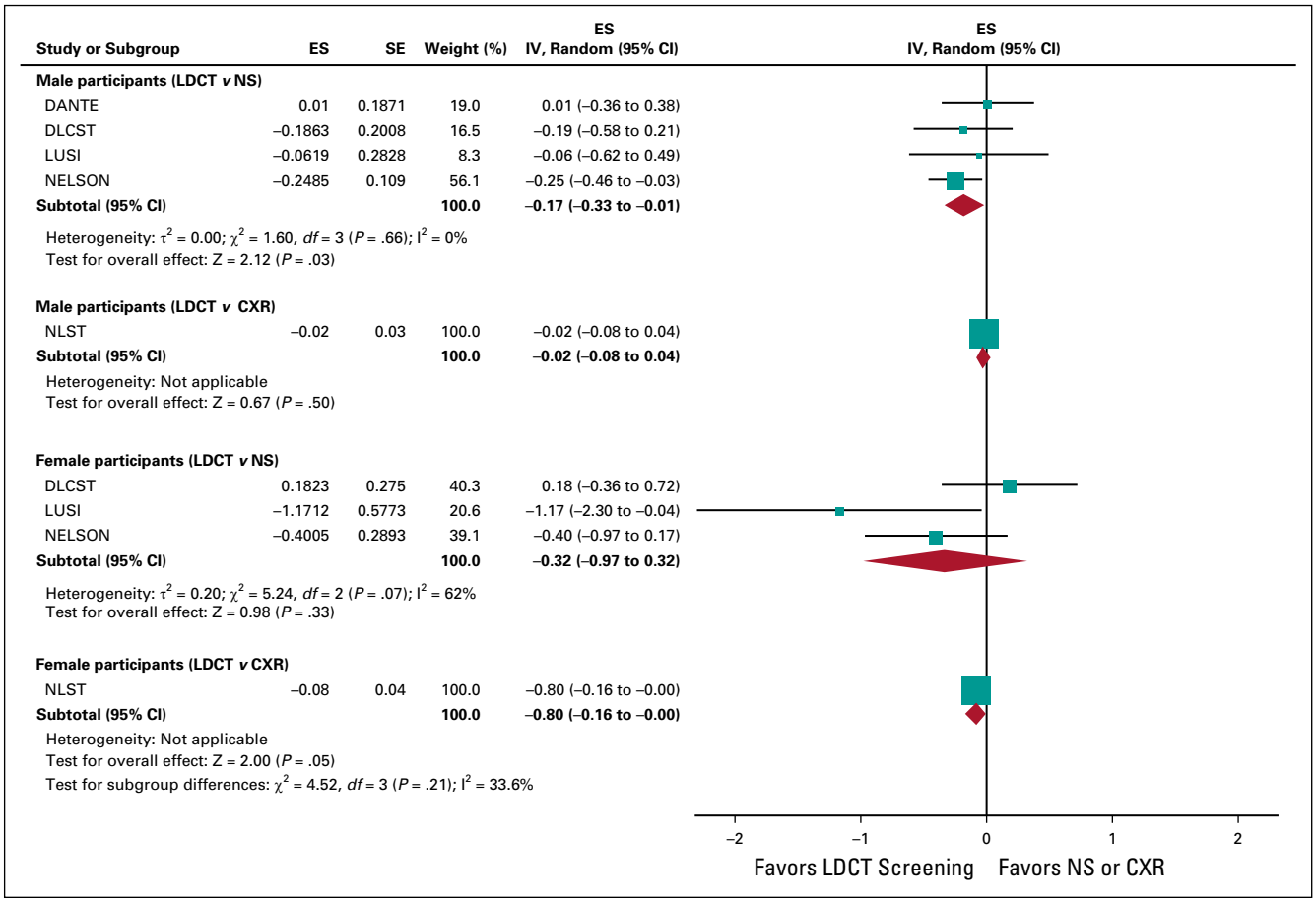

FIG 4. Forest plot showing ES for lung cancer–related mortality in subjects undergoing computed tomography lung screening versus either clinical observation or CXR, stratified by sex. CXR, chest x-ray; ES, effect size; IV, inverse variance; LDCT, low-dose computed tomography; NS, no screening.

to the definition of evidence-based guidelines and shared decision making, worldwide.

Since a 20% reduction of lung cancer mortality is a certain relevant benefit for subjects undergoing CTLS, approximately 38% increase of overdiagnosis could be perceived as a critical barrier to the CTLS implementation. In this regards, it is important to note that the low certainty of evidence for this study outcome, because of the high heterogeneity of included studies in terms of both methodologic approach and follow-up duration, may have likely biased this pooled estimate, leading to a possible overestimation of overdiagnosis. Indeed, as recently shown by the two largest randomized, NELSON and NLST trials,[14,27] the rate of overdiagnosis is critically dependent from the length of follow-up following the final screen, thus dramatically decreasing over the time. Also, the 10-year results of the MILD trial[13] showed that prolonging CTLS beyond 5 years may further enhance its diagnostic performance, suggesting active radiologic surveillance as a valid strategy to reduce unnecessary surgery of slow-growing nodules, which account for the majority of overdiagnosed lung adenocarcinomas. Although our analysis included more than 85,000 participants, it was not adequately powered to detect any difference of all-cause mortality. Of note, the lack of an extended yearly screening in the majority of analyzed studies, as well as the high competing risk of death from other causes, characterizing subjects with smoking attitude, may have also biased the evaluation of this study outcome.

Differently from what observed in the NLST,[28] our subgroup analysis including five[6,8,11,14,28] out of nine trials reporting sex-stratified outcomes revealed no significant differences in terms of lung cancer mortality between men and women. However, the limited number of examined studies does not allow to derive any definitive conclusion. Unfortunately, the slight heterogeneity between trials in terms of published data, regarding subjects' age groups, and smoking history did not allow us to investigate potential differences of screening effects according to such additional variables, thus gathering further research. As recently pointed out by a panel of European experts in the field of thoracic malignancies,[29] identifying high-risk population to be screened, by the use of multivariate risk prediction models, represents a major issue to be

rapidly addressed, to optimize CTLS performance and outcomes for routinely use.

The main limitation of our analysis includes the lack of blinding for the majority of included studies, which may have increased the risk of potential detection bias. Also of note is the heterogeneity of included trials and population, in terms of eligibility criteria and follow-up duration, as well as the differences regarding nodule evaluation methods and screening positivity criteria or intervals. Finally, as partially discussed above, the lack of extended follow-up data regarding yearly screening and overdiagnosis rate among the majority of included studies may have negatively conditioned the results of our analysis, likely leading to an underestimation of benefits along with an overestimation of harms associated with the CTLS.

In conclusion, the results of this work demonstrated that the use of annual CTLS in subjects with a cigarette smoking history produced a relevant reduction of lung cancer–related mortality, burdened by a significant increase of overdiagnosis. Despite there still being uncertainty about overdiagnosis estimate, this meta-analysis suggested that the potential benefits associated with CTLS outweigh harms, ultimately supporting the systematic implementation of lung cancer screening worldwide.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Benefits and Harms of Lung Cancer Screening by Chest Computed Tomography: A Systematic Review and Meta-Analysis

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APPENDIX

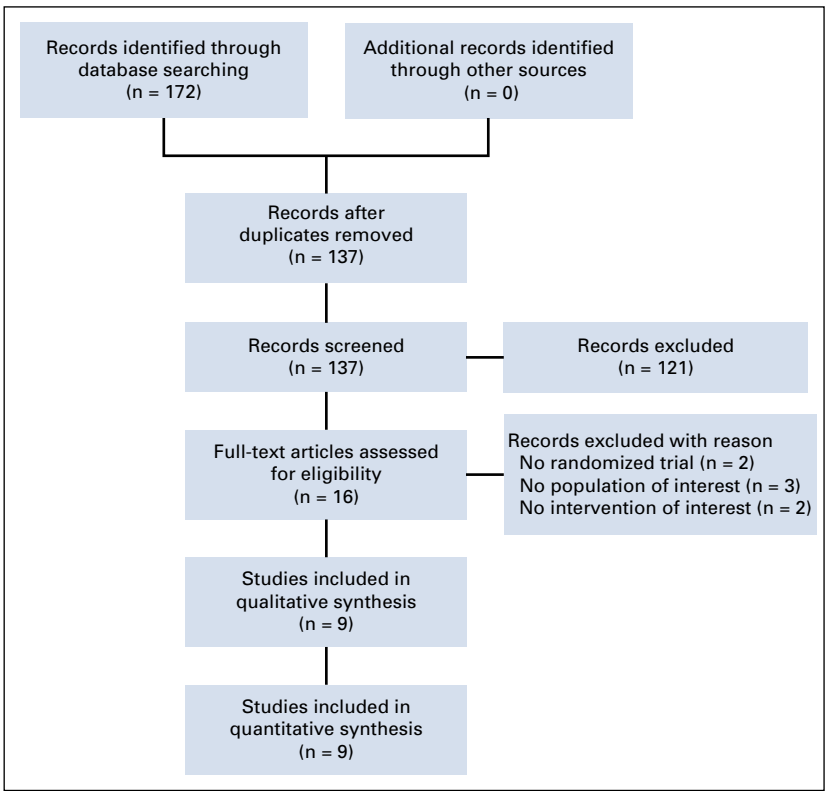

FIG A1. Study selection flowchart.

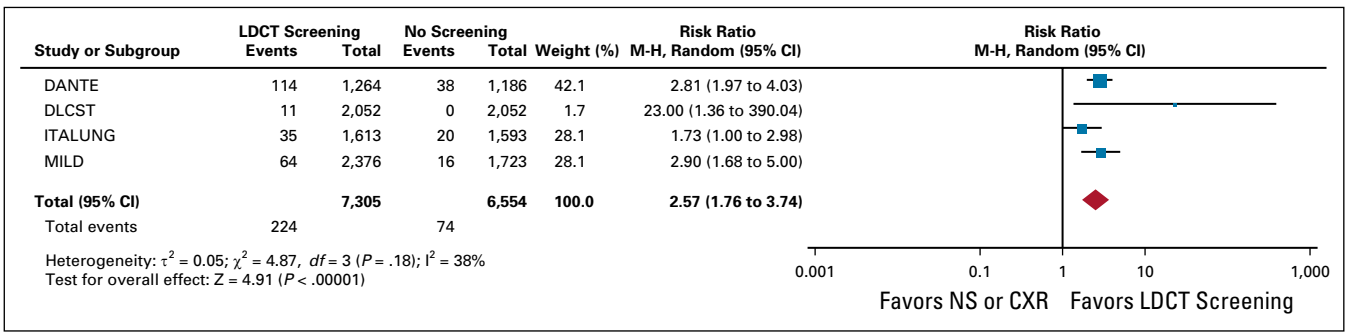

FIG A2. Forest plot showing RR for resectability rate in subjects undergoing computed tomography lung screening versus clinical observation or CXR. CXR, chest x-ray; LDCT, low-dose computed tomography; M-H, Mantel-Haenszel; NS, no screening; RR, risk ratio.

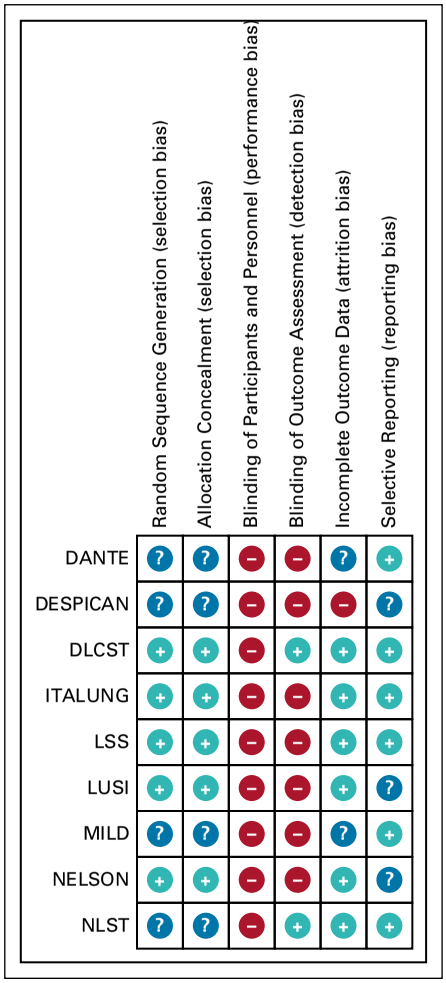

FIG A3. Risk of bias analysis in the included studies.