



Population-Based Screening Using Low-Dose Chest Computed Tomography: A Systematic Review of Health Economic Evaluations

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Accepted: 27 December 2022 / Published online: 20 January 2023
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Abstract

Background Chest low-dose computed tomography (LDCT) is a promising technology for population-based screening because it is non-invasive, relatively inexpensive, associated with low radiation and highly sensitive to lung cancer. To improve the cost-effectiveness of lung cancer screening, simultaneous screening for other diseases could be considered. This systematic review was conducted to analyse studies that published evidence on the cost-effectiveness of chest LDCT screening programs for different diseases.

Methods Scopus and PubMed were searched for English publications (1 January 2011–22 July 2022) using search terms related to screening, computed tomography and cost-effectiveness. An additional search specifically searched for the cost-effectiveness of screening for lung cancer, chronic obstructive pulmonary disease or cardiovascular disease. Included publications should present a full health economic evaluation of population screening with chest LDCT. The extracted data included the disease screened for, model type, country context of screening, inclusion of comorbidities or incidental findings, incremental costs, incremental effects and the resulting cost-effectiveness ratio amongst others. Reporting quality was assessed using the 2022 Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist.

Results The search yielded 1799 unique papers, of which 43 were included. Most papers focused on lung cancer screening ($n = 40$), and three were on coronary calcium scoring. Microsimulation was the most commonly applied modelling type ($n = 16$), followed by life table analysis ($n = 10$) and Markov cohort models ($n = 10$). Studies reflected the healthcare context of the US ($n = 15$), Canada ($n = 4$), the UK ($n = 3$) and 13 other countries. The reported incremental cost-effectiveness ratio ranged from US\$10,000 to US\$90,000/quality-adjusted life year (QALY) for lung cancer screening compared to no screening and was US\$15,900/QALY–US\$45,300/QALY for coronary calcium scoring compared to no screening.

Discussion Almost all health economic evaluations of LDCT screening focused on lung cancer. Literature regarding the health economic benefits of simultaneous LDCT screening for multiple diseases is absent. Most studies suggest LDCT screening is cost-effective for current and former smokers aged 55–74 with a minimum of 30 pack-years of smoking history. Consequently, more evidence on LDCT is needed to support further cost-effectiveness analyses. Preferably evidence on simultaneous screening for multiple diseases is needed, but alternatively, on single-disease screening.

Registration of systematic review Prospective Register of Ongoing Systematic Reviews registration CRD42021290228 can be accessed https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=290228.

1 Introduction

Population-based screening could avoid severe consequences of diseases through early detection and early treatment, thereby improving health outcomes and potentially reducing healthcare costs in the long term [1]. However, large-scale screening requires major upfront investments. Given that healthcare budgets are limited, assessment of the

long-term impact on health outcomes and costs is required to assist public policy decision-making toward the implementation of screening [2].

Low-dose computed tomography (LDCT) is a promising technology for use in population-based screening programs because it is non-invasive, has a low radiation dose and is relatively inexpensive compared to other imaging modalities [3]. Chest LDCT for lung cancer, specifically, has high sensitivity, has been investigated extensively and is recommended for population-based screening by the US

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Key Points for Decision Makers

Literature regarding the health economic benefits of simultaneous low-dose computed tomography (LDCT) screening for multiple diseases is absent.

Evidence on the cost-effectiveness of LDCT screening for cardiovascular disease is very limited and is absent for chronic obstructive pulmonary disease.

More evidence on LDCT for diseases other than lung cancer is needed to support further cost-effectiveness analyses.

Preventive Services Task Force (USPSTF) [4]. In many European countries, nationwide lung cancer screening is currently being investigated but not yet implemented. Previously, two reviews investigated methodological differences between health economic evaluations of LDCT lung cancer screening [5, 6]. Both concluded that there is no consensus on whether LDCT lung cancer screening is cost-effective and that reported conclusions on cost-effectiveness depend heavily on the screening strategy evaluated (e.g. which population was targeted) as well as methodological decisions (e.g. whether overdiagnosis was included in the analysis).

The European Society of Radiology and European Respiratory Society (ESR/ERS) position statement on lung cancer screening additionally stated that researchers still disagree on what the drivers of a cost-effective lung cancer screening program would be [7]. Drivers could include the target population selected, frequency of screening and the inclusion of smoking cessation programs. According to the National Lung Screening Trial (NLST) data from the US, the main driver is the number of computed tomography (CT) scans, showing that the number of extra CT scans for follow-up after a positive screen should be minimised. Furthermore, the position statement mentions that lung cancer screening might have even more value when broadening screening to also include detection of chronic obstructive pulmonary disease (COPD), cardiovascular disease (CVD) and other smoking-related diseases. This suggests that the cost-effectiveness of lung cancer screening with LDCT may be improved by screening for more diseases on a single scan, thereby increasing screening yield with minor additional costs.

Clinical evidence indeed exists showing that LDCT biomarkers can be used to also detect, amongst others, sub-clinical COPD and coronary artery disease [8, 9], or even a wider range of cardiovascular, respiratory and oncological diseases [10]. For health economic evidence, an early health economic evaluation, conducted by our group, estimated the

potential of screening for lung cancer, COPD and CVD in a multi-disease screening program [11], concluding that there is potential value in simultaneously screening for these diseases.

This review aims to analyse the evidence for the cost-effectiveness of population-based screening programs using chest LDCT across a range of diseases, with a specific focus on full health economic evaluations.

2 Methods

2.1 Search Strategy

The systematic review (Prospective Register of Ongoing Systematic Reviews registration CRD42021290228) was conducted by searching in Scopus and PubMed, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12]. The focus of the search strategy was to identify articles and scientific reports describing full health economic evaluations on CT-related population-screening programs. Search terms were kept broad, to ensure that all relevant literature was included, such as searching for “computed tomography” although the inherent focus of this paper is *chest* LDCT. In addition, to ensure that important studies were not missed in the search, a second set of search strategies was used to search for the cost-effectiveness of screening for diseases that are known to have screening potential using CT (lung cancer, COPD and CVD) without specifying CT. Only studies from the last 10 years before the start of this systematic review have been included due to significant changes in treatment, especially for lung cancer. The search strategy was reviewed by an information specialist and included articles in English, from 1 January 2011 to 22 July 2022.

Health economic evaluations were identified by including search terms similar to those used by Degeling et al. such as cost-effectiveness analysis, cost-utility analysis, cost-benefit analysis, decision analytical model and economic evaluation [13]. Overall, a variety of terminology was included. Studies that were familiar to the authors before the search as well as the reference lists of systematic reviews identified with the search were used in combination with the final set of publications of these studies to verify that the search strategy identified all relevant papers. Therefore, reviews were included in the search strategy, but not in the final set of included studies. Articles, conference papers and reviews were included, and editorial letters, notes, book chapters, short surveys and special reports were excluded. The search strategies were discussed with an information specialist and can be found in Online Resource Table 1 (see the electronic supplementary material).

2.2 Inclusion and Exclusion

Studies were screened to include full health economic evaluations of population-based screening using chest CT. Full health economic evaluations required the reporting of incremental costs and health outcomes of screening strategies or total costs and health outcomes from which the incremental values could be derived. Population-based screening was defined as screening focusing on target groups that are not limited to a patient group, but consist of a group of individuals at risk of a certain disease. Therefore, studies investigating a screening policy within an already existing patient group were excluded. All abstracts were screened independently by the first reviewer (CB) and a random sample of 10% by a second reviewer (MOW). If it was not clear from the title and abstract if a study should be included, the study was labelled as relevant for full-text assessment. Studies on which the reviewers did not agree were discussed until consensus was reached. The first reviewer screened all studies included in the full-text assessment. The second reviewer screened a random sample of 10% and another 10% that the first reviewer identified as challenging cases. All disagreements within the 20% sample were discussed with a third reviewer (HK) until consensus was reached.

2.3 Data Extraction

Information was extracted from included papers by one reviewer (CB) using Covidence online software for systematic reviews [14], and all unclear extractions were discussed between all reviewers (CB, MOW, HK). Extractions included general information such as the authors, journal name, year, country and aim of the study. Information extracted about screening included diseases screened for, recurrence of screening, starting and stopping age of screening and other disease-specific population descriptions. Modelling decisions were extracted such as model type, study perspective, comparator strategy, time horizon, discount rate, treatments in the care pathway and which co-occurring diseases and incidental findings were included. Evidence extracted as used in the simulation model included screening costs, sensitivity, specificity and participation rates. Finally, results were extracted, including (1) the subgroup(s) within the target population being considered, (2) incremental health outcomes and costs, (3) the incremental cost-effectiveness ratio (ICER) of the most cost-effective strategy, (4) the comparator, (5) which willingness-to-pay (WTP) threshold the results were compared to and (6) the conclusion on whether or not the best-performing strategy was considered cost-effective. The reported ICER values are either the final reported base case value or the most cost-effective result when multiple strategies are compared in the main

analysis (not considering results from the sensitivity analysis). Incremental costs and effects were reported as found in the respective studies or calculated as the difference between the total costs and effects of the intervention and no screening or another comparator. If the total incremental costs and effects were reported, it was converted to per person costs and effects to be able to compare outcomes across countries with different population sizes. The cost-effectiveness conclusions were reported as found in the respective studies and, if not reported, the ICERs were compared to the WTP threshold reported. The reported incremental costs associated with the reported ICERs were expressed in 2021 values of the local currency using the local inflation rates and subsequently converted to US dollars using the average exchange rate from November 2021. US dollars have been used as a reporting currency, as it is easily interpretable by readers from different countries.

Heterogeneity and bias in the results from different studies were not evaluated in this paper, due to expected variability in methods used. This paper focuses on providing a narrative synthesis and comparison of studies.

2.4 Quality Assessment

The reporting quality of all papers included in the final set was assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist [15]. This checklist contains 28 reporting criteria, which were scored with 0, 1 or not applicable, based on which the reporting of studies was classified as high (> 85%), medium (60–85%) or low quality (< 60%).

3 Results

3.1 Search Results

The search strategy yielded 1799 unique studies as shown in the PRISMA flowchart, Online Resource Fig. 1 (see the electronic supplementary material). Screening title and abstract resulted in 62 studies for full-text assessment. During this assessment, studies were excluded if they did not present a full health economic evaluation ($n = 7$), full texts were not available in English ($n = 9$) and studies did not report, and did not allow the calculation of, incremental health outcomes and costs of screening ($n = 4$). The remaining 43 studies were included for data extraction, of which the most important information can be found in Table 1.

3.2 General Characteristics

The general characteristics of all studies are summarised in Online Resource Table 2 (see the electronic supplementary material). All studies focused on lung cancer screening ($n = 40$, 93%) apart from three studies on CVD (7%) [16, 17]. One study included used CT calcium scoring but then focused the health economic analysis only on identifying incidental pulmonary nodules to detect lung cancer [18]. This study was therefore considered a lung cancer screening study. Studies focused on the healthcare context of the US ($n = 15$, 35%), Canada ($n = 4$, 9%), the UK ($n = 3$, 7%) and 13 other countries, with some countries investigated more than once. The CHEERS score for reporting quality ranged from 37% to 100%, with 20 studies (47%) classified as high quality, 20 (47%) as medium quality and three (7%) as low quality. Online Resource Fig. 2 displays the proportion of studies that reported each item on the CHEERS checklist. No considerable conclusions could be drawn between the reporting quality of the studies and their methods or conclusions. However, it is striking that no studies included a health economic analysis plan, which is an addition to the 2022 checklist. Studies considered target screening populations from the age of 45 up to 100. The minimum number of pack-years of smoking to be eligible for lung cancer screening ranged from 20 to 40. However, some studies had no specific requirement on the minimum number of pack-years smoked ($n = 10$), of which two used risk assessment to identify the eligible population. The maximum number of years since smoking cessation for former smokers to be eligible for screening was 10 or 15 years, while some studies had no smoking cessation requirements ($n = 19$, 44%) and some studies only screened current smokers ($n = 4$, 9%). Two studies investigated the cost-effectiveness of screening in China and Japan, respectively, including non-smokers due to the lower proportion of lung cancer cases attributed to smoking [19, 20]. Two of the three CVD studies included asymptomatic individuals aged 40–85 with intermediate risk based on the Framingham risk score, and the third included individuals aged 40–70 with a family history coronary artery disease events.

Figure 1 illustrates the screening strategies that were considered to be the most cost-effective and are ordered firstly alphabetically according to the country of the study context followed by the surname of the first author. The vertical lines indicate at which ages screening takes place. From this figure, it is clear that there is a consensus on the age (55–74) and frequency (annually) of screening. However, this consensus is likely partially artificial given that the majority ($n = 25$, 58%) of studies use NLST data (in combination

with national survival data or other, smaller trials) and therefore reflect the NLST inclusion criteria in the definition of their screening strategy. The eligibility criteria of this trial were current and former smokers aged 55–74 with ≥ 30 pack-years smoked or who stopped smoking within 15 years from the start of screening. One study investigating the cost-effectiveness of lung cancer screening separately for men and women concluded that men should be screened annually between the ages of 55 and 80 and women should be screened biennially between the ages of 50 and 80 [21], and another concluded that screening is only cost-effective in men [19].

3.3 Modelling Choices

Modelling choices are summarised in Online Resource Table 3 (see the electronic supplementary material). Microsimulation was the most common model type ($n = 16$, 37%), followed by life table analysis ($n = 10$, 23%), Markov cohort models ($n = 10$, 23%), decision trees ($n = 4$, 9%), discrete event simulation ($n = 2$, 5%) and multistate risk model ($n = 1$, 2%). In general, the reasoning behind the choice of model type in the publications was limited. Only ten studies discussed the choice of model type. Most studies reportedly applied a public health or public payer perspective ($n = 25$, 58%), followed by a societal perspective ($n = 10$, 23%) and a commercial health insurer perspective ($n = 6$, 14%) or did not report any perspective ($n = 2$, 5%). The time horizons applied were lifetime (until death) ($n = 23$, 53%) or 5, 10, 15, or 20 years ($n = 10$, 23%). In the other cases ($n = 10$, 23%), the applied time horizon was not reported explicitly.

The majority of studies did not include incidental findings, co-occurrence of other diseases or comorbidities ($n = 35$, 81%) in the cost-effectiveness model. One study [22] mentioned that incidental findings with potential clinical implications from the NELSON (Dutch-Belgian Lung cancer screening) trial were reported [23] without significant impact on morbidity and mortality, and therefore did not include such findings in the model. Four studies [24–27] included only the additional (diagnostic) costs of incidental findings. Only one study [18] included both health effects and costs of incidental findings in their model. This study evaluated the cost-effectiveness of screening for incidental pulmonary nodules in the part of the lung that was screened during cardiac CT calcium scoring [18]. Although this study defined the pulmonary nodules as being incidental because the scan was intended for calcium scoring, only results and outcomes of lung cancer screening were included in the model. In general, the stated reason not to include the effect of incidental findings or comorbidities was a lack of evidence.

Table 1 Summary of included studies

Study	Country	Model type	Screening cost	Screening costs covers	Incremental costs	Incremental effects	Number of (modelled) screenees	ICER (or most cost-effective scenario)	ICER US\$ (2021)	WTP threshold	Cost-effective?
Black (2014) [24] ^a	United States	Implicit: life table analysis	\$1,130 pp	Indirect costs: time and travel for participant and caregiver	US\$1,631 pp	0.0201 QALY pp 0.0316 LYG pp	54,452	US\$81,000/QALY US\$2,000/LYG	\$103,680/QALY \$66,560/LYG	US\$100,000/QALY	Yes
Black (2015) [37] ^a	United States	Implicit: life table analysis	\$1,130 pp (incl. \$101 for travel)	Indirect costs: time and travel for participant and caregiver	US\$1,631 pp	0.0201 QALY pp 0.0316 LYG pp	26,642	US\$81,000/QALY US\$2,000/LYG	\$103,680/QALY \$66,560/LYG	US\$100,000/QALY– US\$150,000/QALY	Yes
Cadham (2021) [38] ^a	United States	Microsimulation	\$271.44	CT scan	US\$0.44 pp*	0.0082 QALY pp*	Modelled 1 million men, 1 million women	US\$55/QALY*	\$555/QALY*	–	Yes
Cressman (2017) [39] ^a	Canada	Markov cohort model	\$157–474	Unclear	US\$668 pp	0.32 QALY pp	49,775 individuals in dataset	US\$20,724/QALY	\$23,625/QALY	US\$100,000/QALY	Yes
Criss (2019) [40] ^a	United States	Microsimulation	\$271.44	CT scan	US\$870,000,000	1,990 QALY 2,650 LYG	Modelled 1 million men, 1 million women	US\$49,200/QALY US\$36,400/LYG	\$53,628/QALY \$39,676/LYG	US\$100,000/QALY	Yes
Diaz (2021) [41] ^a	Spain	Microsimulation	€175	LDCT scan	€191 pp	0.04032 QALY pp	100,000 theoretical cohort of men	€4,732/QALY	\$5,300/QALY	€22,000– €25,000/QALY	Yes
Du (2020) [21]	Netherlands	Microsimulation	Stage I–III = €39,993; stage IV = €58,640	CT scan, diagnosis, treatment	€2311/man; €1432/woman	0.06776 LYG/man 3.62181 LYG/women	Simulated 100,000 men and 100,000 women	€27,600/LYG men €21,100/LYG women	\$28,246/LYG	€60,000/LYG	Yes
Du 2022 [19]	China	Microsimulation	¥550	CT scan	¥3800/man	0.0221 LYG/man	Simulated 100,000 men and 100,000 women	¥192,600/LYG men; not cost-effective for women	\$28,890/LYG	¥217,300/LYG	Yes
Esmaili (2021) [42]	Iran	Markov cohort model	IRR2,436,466 per LC case	CT scan	IRR2,681,590 pp	0.02722 QALY pp	–	IRR98,515,014/QALY	\$3,790/QALY	3 × GDP per capita, value not given	Yes

Table 1 (continued)

Study	Country	Model type	Screening cost	Screening cost covers	Incremental costs	Incremental effects	Number of (modelled) screenees	ICER (or most cost-effective scenario)	ICER US\$ (2021)	WTP threshold	Cost-effective?
Evans (2016) [43] ^a	Canada	Discrete event Monte Carlo micro-simulation interpreted as DES	At start-up, the annual cost of screening is estimated at CAN\$75 million, rising to CAN\$128 million in 10 years	Does not include the costs of promoting the program, additional overhead or infrastructure costs, or setting up the information systems necessary to monitor the effects of the program	CAN\$2,170,800,000	51,300 LYG	1.4 million reducing to 1.2 million (2014–2023) eligible for screening; average screened annually (2014–2023) = 323,200	CAN\$42,316/LYG	\$14,962/QALY	CAN\$100,000/QALY	Yes
Field (2016) [44]	UK	Implicit: life table analysis	£282,490 total for CT scans	CT scan	£272 pp	0.03 QALY pp	28,000	£8,466/QALY	\$14,962/QALY	–	No conclusion
Fitzgerald (2015) [45] ^a	United States	Microsimulation	–	CT scan, physician visits related to screening	CAN\$1,066,100,000	42,000	–	CAN\$25,400/QALY	\$24,895/QALY	CAN\$32,000/QALY	Yes
Goffin (2015) [46] ^a	Canada	Microsimulation	–	CT scan	CAN\$2,700,000,000	51,000 QALY 130,000 LYG	–	CAN\$52,000/QALY	\$50,965/QALY	1 × GDP = CAN\$47,000; 3 × GDP = CAN\$141,000	No
Goffin (2016) [47] ^a	Canada	Implicit: decision tree	–	Recruitment (perhaps others, unclear)	CAN\$1,500,000,000	46,000 QALY	1.4million	CAN\$33,000/QALY	\$32,343/QALY	–	No conclusion
Gómez-Carballo (2022) [48]	Spain	Markov cohort model	€142	GP visit, CT scan and screening campaign	€59 pp [†]	0.025 QALY pp [†] 0.024 LYG pp [†]	2.8 million	€2,720/QALY	\$2720/QALY	€25,854/QALY	Yes

Table 1 (continued)

Study	Country	Model type	Screening cost	Screening costs covers	Incremental costs	Incremental effects	Number of (modelled) screenees	ICER (or most cost-effective scenario)	ICER US\$ (2021)	WTP threshold	Cost-effective?
Hinde (2018) [49]	UK	Deterministic cohort model (UKLS method) interpreted as Markov cohort model	Per individual = £565; total costs = £566,013	Recruitment, lung health checks, initial CT scan and report, 3-month CT and report	£663,076	65.85 QALY 88.13 LYG	1384	£10,069/QALY £7,524/LYG	\$15,588/QALY \$11,6479/LYG	£20,000/QALY	Yes
Hofer (2018) [28]	Germany	Two cohort Markov models combined	€68.88 + €30 = €98.88	Scan, radiologist consult and additional costs of structured screening programs, such as documentation and invitation	€1,153 pp	0.04 QALY pp 0.06 LYG pp	1,600,270	€30,291/QALY €19,302/LYG	\$36,894/QALY \$23,510/LYG	€48,000/QALY	Yes
Jaine (2018) [25] ^a	New Zealand	Markov macro-simulation stage shift model: interpreted as Markov cohort model	Not provided	Invitation, administration time to identify target population, screening test, incidental findings	US\$2,842 pp	0.067 QALY pp	-	US\$44,000/QALY	\$53,680/QALY	US\$30,000/QALY	No
Jiang (2020) [18] ^a	United States	Decision tree	Only CT	CT scan	US\$276 pp	0.03 QALY pp	-	US\$10,447/QALY	\$10,172/QALY	US\$50,000/QALY	Yes
Kanarkiewicz (2015) [50] ^a	Poland	Implicit: life table analysis	€50	CT scan	€4.33pp [†]	0.003195 QALY pp [†]	-	€1353/LYG	\$1649/LYG	€27,845/LYG	Yes

Table 1 (continued)

Study	Country	Model type	Screening cost	Screening costs covers	Incremental costs	Incremental effects	Number of (modelled) screenees	ICER (or most cost-effective scenario)	ICER US\$ (2021)	WTP threshold	Cost-effective?
Al Khatat (2022) [51]	Netherlands	Markov cohort model	€174	CT scan	€9,914,408	668.6 QALY	100,000 simulated	€14,828/QALY	\$17,372/QALY	€20,000/QALY	Yes
Kowada (2022) [20]	Japan (J) & United States (US)	Markov cohort model	J: US\$196; US: US\$255	CT scan	J: -US\$135,575 pp; US: US\$7,484 pp	J: 0.78445 QALY, 0.7455 LYG US: 0.00155 QALY, 0.0021 LYG	J: 13.05 million; US: 31.88 million	J: negative US: US\$2,549,637/QALY US: \$1,841,621/QALY	J: negative US: US\$100,000/QALY	US\$100,000/QALY	J: Yes US: No
Kumar (2018) [52] ^a	United States	Implicit: microsimulation	US\$255	CT scan	US\$1,089 pp	0.0195 QALY pp 0.0355 LYG pp	26,722 patients in data	US\$60,000/QALY US\$37,000/LYG	\$65,400/QALY \$40,330/LYG	US\$55,000/QALY	No
McLeod (2020) [26]	New Zealand	Markov macro-simulation: interpreted as Markov cohort model	NZ\$400 + NZ\$30 = NZ\$430	CT scan and invitation	NZ\$105,000,000	3230 HALY	-	NZ\$34,400 (NZ\$24,700 - NZ\$39,100)/HALY	\$24,668/LYG	NZ\$45,000/HALY	Yes
McMahon (2011) [53]	United States	Microsimulation	-	-	US\$2708 pp	0.0155 QALY pp	500,000	US\$236,925/QALY	\$168,750/QALY	-	No conclusion
Pyenson (2012) [54]	United States	Life table analysis (actuarial methods)	US\$247 pp screened	Unclear, seems like only scan	US\$4,400,000,000	-	18,192,966	US\$18,862/LYG	\$22,446/LYG	US\$19,000/LY saved	Yes
Pyenson (2014) [55]	United States	Life table analysis (actuarial methods)	US\$241 pp screened (including coverage of invited)	-	US\$41,647,811,614	2,257,053 LYG	4,894,329	US\$18,452/LYG	\$21,958/LYG	-	No conclusion
Shmueli (2013) [56]	Israel	Decision analytic framework (decision tree)	US\$74	CT scan	US\$86.47 pp	0.059082 QALY pp	-	US\$1,464/QALY	\$1,786/QALY	US\$10,000/QALY	Yes

Table 1 (continued)

Study	Country	Model type	Screening cost	Screening costs covers	Incremental costs	Incremental effects	Number of (modelled) screenees	ICER (or most cost-effective scenario)	ICER US\$ (2021)	WTP threshold	Cost-effective?
Snowsill (2018) [57] ^a	UK	Decision tree and DES	2.9 + 18 + 54 + 1.74 + 6.25 + 98.8 = £181.69 pp	Invitation and questionnaire, scoring of questionnaire, follow-up letter, nurse consultation, CT scan	£23 pp	0.0008 QALY pp	1.3 million	£28,169/QALY	\$43,223/QALY	£20,000/QALY	No
Sun (2021) [58]	China	Markov model (individual level) interpreted as micro-simulation	US\$68	Assumed to be scan only	US\$132,660,000	10.160 QALY	Modelled 100,000	US\$13,057/QALY	\$14,232/QALY	US\$29,306/QALY	Yes
Tabata (2014) [59]	Japan	Inuma's calculation model (no further details found in English)	-	-	¥2,016,000,000	6.530 LYG	-	¥268,000-¥1,942,000/LYG	\$5,780/LYG	¥6,000,000/QALY	No
Ten Haaf (2017) [22] ^a	Canada	Microsimulation	CAN\$107	Invite to risk assessment, risk assessment, GP visit, screening invite	CAN\$58,550 pp	1.489 LYG pp	-	CAN\$41,136/LYG	\$45,601/LYG	US\$41,114/LYG or CAN\$50,000	Yes
Tomonaga (2018) [60] ^a	Switzerland	Microsimulation	€386 (CT or follow-up)	Centralised invitation and CT scan	€88,362,204 per 100,000 alive individuals	1.009 LYG per 100,000 alive individuals	2.8 million	€34,159/LYG	\$30,416/LYG	€50,000/LYG	Yes

Table 1 (continued)

Study	Country	Model type	Screening cost	Screening cost covers	Incremental costs	Incremental effects	Number of (modelled) screenees	ICER (or most cost-effective scenario)	ICER US\$ (2021)	WTP threshold	Cost-effective?
Toumazis (2019) [61] ^a	United States	Microsimulation	–	–	US\$1,236 pp	0.0199 QALY pp	106,858–279,416	US\$62,154/QALY	\$67,748/QALY	US\$100,000/QALY	Yes
Treskova (2017) [62] ^a	Germany	Microsimulation	–	–	€2,232,000,000	133,222 LYG	–	€16,754–€24,160/LYG	\$20,989/LYG	€30,000/LYG	Yes
Van Kempen (2011) [16]	United States	Markov cohort model	US\$105	Calcium scoring	US\$4,670 pp	0.13 QALY pp	576	US\$35,919/QALY	\$45,258/QALY	US\$50,000/QALY	Yes
Van Kempen (2016) [17]	United States	Microsimulation	US\$20 up to US\$325 + US\$80	Obtaining Framingham risk factors including blood panel and physician visit	US\$328 pp	0.01 QALY pp	3736	US\$32,800/QALY	\$37,392/QALY	–	Yes
Venkataraman (2021) [27]	United States	Microsimulation	US\$374	CT scan, clinical review, lipid test, radiation induced cancer treatment and incidental finding costs	US\$145 pp	0.0097 QALY pp	1083 individuals in dataset	US\$19,683/QALY	\$15,914/QALY	US\$50,000/QALY	Yes
Veronesi (2020) [63] ^a	Italy	Decision tree	\$80	Scan + administrative and operating costs of screening	€225 pp	0.087 LYG pp	–	€2,944/LYG €3,297/QALY	\$4,350/QALY \$3,950/LYG	€25,000/LYG	Yes
Villanti (2013) [64] ^a	United States	Life table analysis (actuarial methods)	–	CT scan	\$27,824,282,242	985,284 QALY	18 million	US\$23,826/QALY– US\$47,115/QALY	\$33,606/QALY	US\$50,000 per QALY	Yes

Table 1 (continued)

Study	Country	Model type	Screening cost	Screening costs covers	Incremental costs	Incremental effects	Number of (modelled) screenees	ICER (or most cost-effective scenario)	ICER US\$ (2021)	WTP threshold	Cost-effective?
Wade 2018 [65] ^a	Australia	Implicit: Life table analysis	–	–	AU\$1,564 pp	0.0067 QALY pp 0.0113 LYG pp	53,171	AU\$233,000/ QALY AU\$138,000/ LYG	\$190,478/ QALY \$112,815/ LYG	AU\$50,000/ QALY	No
Yang (2017) [66] ^a	Taiwan	Implicit: life table analysis	–	–	US\$22,755	1.16 QALY	62,392	US\$19,683/ QALY	\$23,226/ QALY	US\$20,925/ QALY	Yes
Zhao (2022) [67]	China	Markov cohort model	¥246	CT scan	–¥321.16 pp	0.15 QALY 1.425 LYG	10,000 simulated	–¥26,796/ QALY	–\$4,019/ QALY	¥212,676	Yes

– not reported, AU\$ Australia dollars, CAN\$ Canadian dollars, CT computed tomography, DES discrete event simulation, GDP gross domestic product, GP general practitioner, HALY health-adjusted life year, ICER incremental cost-effectiveness ratio, IRR Iranian rial, J Japan, LC lung cancer, LDCT low-dose computed tomography, LY life year, LYG life years gained, NZ\$ New Zealand dollars, NLST National Lung Screening Trial, pp per person, QALY quality-adjusted life year, UKLS United Kingdom Lung Screen, WTP willingness-to-pay

* Screening with smoking cessation compared to screening without smoking cessation

† Converted from cost or effect per lung cancer patient to cost or effect per screened individual, by dividing by the proportion of lung cancer patients

^aStudies that used data from NLST

3.4 Modelling Evidence and Parameters

The parameters used for modelling, including their values, are given in Online Resource Table 4 (see the electronic supplementary material). Only 21 studies (49%) included non-perfect screening participation rates in the base case or the sensitivity analysis. This means that half of the studies assumed 100% participation, which is unrealistic for any screening program, or, less likely, implemented a lower participation rate without reporting it.

The cost of screening varied greatly, from \$37 to \$1232 after conversion, as some models only included the cost of an LDCT scan and others included additional costs such as invitations to screening, database management and overhead screening costs. All costs are reported in their original currency in Online Resource Table 4. Sensitivity and specificity values for LDCT used in the model were not reported in 14 studies (33%); 18 studies (42%) explicitly stated the sensitivity and specificity values used, of which five reportedly included sensitivity and specificity based on the NLST. Nine Studies (21%) only reported a false positive rate, and two studies (5%) reported the included sensitivity, but not specificity. Five of the studies included sensitivity values depending on the size of the nodule and the stage of disease, respectively [21, 28]. Reported sensitivity values ranged between 43% and 100% and specificity between 62 and 99%.

3.5 Economic Evaluation Results

The results and conclusions of all included studies are summarised in Online Resource Table 5 (see the electronic supplementary material). The reported incremental costs and effects per screened individual were used or were calculated based on the total costs and effects reported. Most of the studies ($n = 33$, 77%) concluded that the evaluated screening program would be cost-effective. For lung cancer screening, the ICERs ranged from –\$4019/LYG to \$113,800/LYG and \$190,500/quality-adjusted life year (QALY) compared to no screening and six other comparators (2021 US\$). The ICERs for cardiac CT calcium scoring were \$15,900/QALY, \$37,400/QALY and \$45,300/QALY compared to no screening (2021 US\$). Studies evaluating lung cancer screening compared to no screening are plotted in Fig. 2 for studies reporting LYG and Fig. 3 for studies reporting QALYs. Studies with negative ICERs were excluded from the figures to support readability. The negative ICERs were driven by a decrease in incremental cost of screening. The country indicated on the plot indicates the context of the study. In these figures, the colour indicates whether a study is cost-effective either based on the reported conclusion or, if not reported, based on comparing reported results with the study-specific WTP threshold.

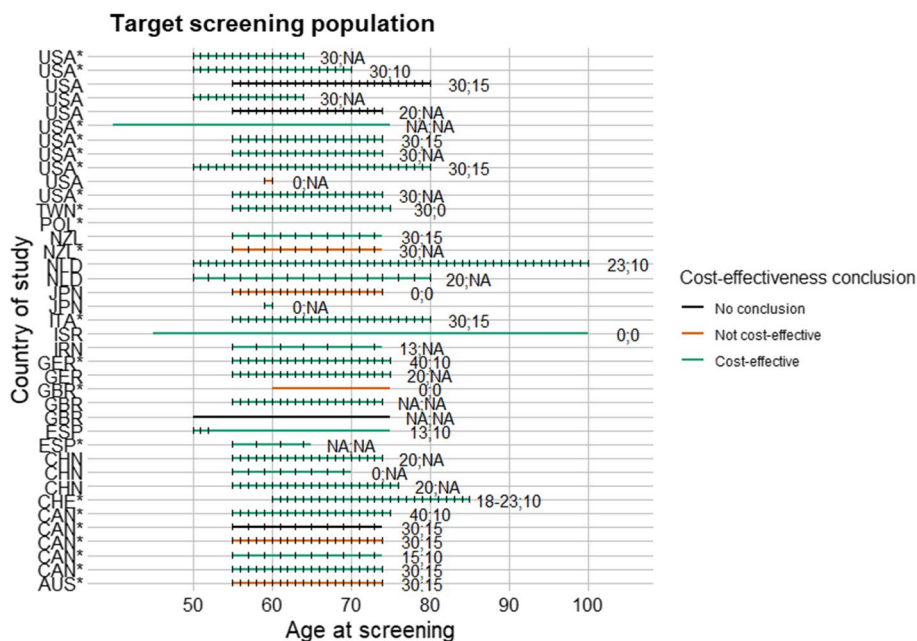


Fig. 1 Visual representation of the age of the target screening population for lung cancer screening. A continuous line represents on-off screening as each black vertical line indicates a screening round. At the end of each study, the smoking requirements are shown. “30;10” indicates > 30 pack-years smoked and < 10 years since cessation. “0;0” indicates that there were no minimum number of pack-years and 0 years since smoking cessation (only current smokers). “NA;NA” indicates that minimum pack-years is not applicable

because smoking was not a requirement (in studies that use a risk calculator to identify eligible individuals) and no maximum years since smoking cessation in the eligible population. Whether a screening strategy is classified as cost-effective or not was firstly based on the reported study conclusion or, if no conclusion was presented, by comparing the base-case results in the paper with the provided willingness-to-pay threshold. *NLST* National Lung Screening Trial. *NA* not applicable. *Study based (partially) on NLST data

4 Discussion

This systematic review presents and analyses the reported evidence of full health economic evaluations on the cost-effectiveness of screening programs using chest LDCT without limiting the evidence to a specific disease. All but three studies evaluated lung cancer screening; the others evaluated coronary calcium scoring using LDCT for CVD. A limited number of studies included co-morbidities, co-occurrences of diseases or incidental findings in their cost-effectiveness models. One of the studies evaluated screening for incidental detection of pulmonary nodules using full chest CT calcium scoring [18], which is the only study that suggests multi-disease screening even though the cost-effectiveness model only covers the costs and benefits of detecting pulmonary nodules. Thus, while a recent early health economic analysis with limited data suggested that extending LDCT screening for lung cancer with screening for emphysema and CVD may be valuable [11], full health economic evidence of the impact of multi-disease screening with LDCT on cost-effectiveness is absent. Multi-disease modelling is also of increasing interest in the field of blood-based (genomic) biomarkers, as explored in recent studies [29, 30]. Additionally, the effects of incidental findings were rarely modelled, because

of a lack of evidence. Increasing attention to COPD and coronary calcium and especially the effect of smoking cessation programs included in lung cancer screening programs, such as the Yorkshire Enhanced Stop Smoking (YESS) study, will likely provide more evidence in this regard [31].

The ERS/SER position statement also suggests broadening screening to include COPD, CVD and other smoking-related diseases, but based on this systematic review, such multi-disease screening programs are not yet reflected in the current health economic evidence. It is expected that the reason for this lack of health economic evidence is very likely due to a lack of clinical evidence for multi-disease screening. Other than the limited evidence on the cost-effectiveness of screening for CVD using LDCT, no health economic evaluation was found investigating the value of COPD screening using LDCT. The current standard of detection of COPD is spirometry, which is cheap, simple and gives an immediate result [32]. Although this explains the absence of health economic evaluations of screening for COPD using LDCT, health economic evidence on the potential value of adding screening for COPD to lung cancer screening is still lacking even though clinical evidence is increasing [33–35].

There was substantial variation in study outcomes caused by, firstly, the different healthcare contexts in which

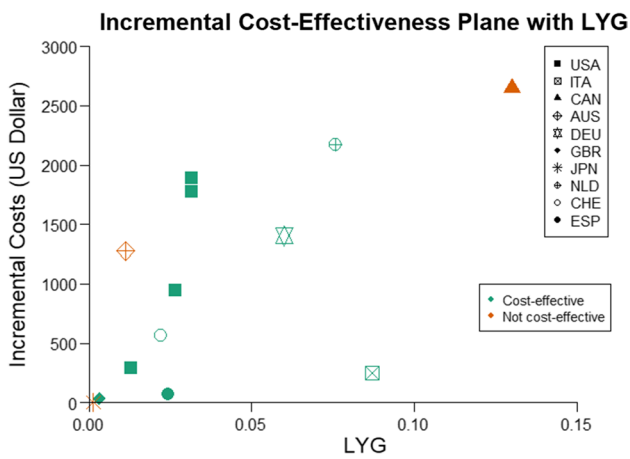


Fig. 2 Lung cancer screening incremental cost-effectiveness plane with LYG per person plotting each study, indicating the context country. Whether a screening strategy is classified as cost-effective or not was firstly based on the reported study conclusion or, if no conclusion was presented, by comparing the base-case results in the paper with the provided willingness-to-pay threshold. *LYG* life years gained

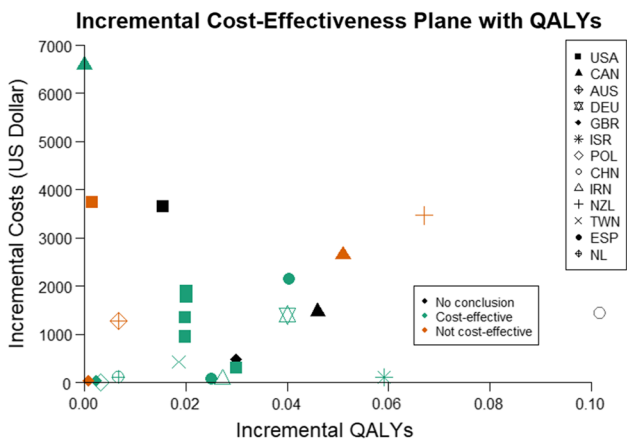


Fig. 3 Lung cancer screening incremental cost-effectiveness plane with incremental QALYs per person plotting each study, indicating the context country. Whether a study is classified as cost-effective or not was firstly based on the reported study conclusion or, if no conclusion was presented, the base-case results were compared to the provided willingness-to-pay threshold. *QALY* quality-adjusted life year

the analyses are conducted, secondly, the different modelling methods used and, thirdly, the difference in input and assumptions made, among others. A microsimulation with a public health perspective, 3% discount rate and a lifetime horizon was most commonly used. Analyses were conducted in the healthcare contexts of 15 different countries, which are not easily transferable between healthcare contexts due to differences in clinical guidelines and cost of healthcare procedures. Only some studies included screening costs broader than only the LDCT scan, such as invitation costs

and costs to store and secure personal data, which are unavoidable costs. Moreover, only a few studies acknowledged that a screening participation rate of 100% is not achievable. It is assumed perfect participation is unrealistic given the limited evidence on real-world participation. For example, screening participation of eligible smokers in the US was 7.3%, while at least 40% participation would be required for a cost-effective screening program [36]. Since only two studies were found on the health economic evaluation for diseases other than lung cancer, results from this study overlap with results of previous systematic reviews focusing purely on health economic evaluations of LDCT lung cancer screening [5, 6]. This review confirms the conclusions of these previous reviews that studies are heterogenous in the healthcare setting, the screening intervals and the methods used for analysis. In contrast with these previous reviews, this review highlights the large overlap in target screening population between different health economic evaluations although the most cost-effective target screening population is not the same across all health economic evaluations. This review does not have a large focus on screening and modelling consequences such as overdiagnosis, lead-time bias and length bias and, rather, adds to the literature by highlighting the importance of incorporating screening participation rates in cost-effectiveness studies and by providing a more up-to-date review and an insightful comparison of the different target populations considered, and, most importantly, based on the aim of reviewing literature for screening for any disease, this review highlights the gap in literature for health economic evaluations of multi-disease screening using CT.

In contrast to the large variation in health economic outcomes, researchers largely agree on the target screening population for LDCT lung cancer screening. However, this agreement could partially be artificial due to the limited availability of data to use in health economic models evaluating lung cancer screening. Most of the studies used data from the NLST trial and therefore the large agreement of the target screening population also corresponds with the NLST criteria of current and former smokers aged 55–74 with a minimum of 30 pack-years of smoking history [24]. Some studies aimed to identify the target population in which screening is most cost-effective within the NLST criteria, concluding that more strict criteria did not result in improved cost-effectiveness. Even studies without NLST data as input decided upon the NLST screening criteria as the target population.

The limitations of this current review are, first, that the CHEERS checklist is primarily intended as a reporting checklist and was not developed to assess the methodological quality of evaluations. However, as reporting quality is likely correlated with the quality of the evaluation itself, it has been used in multiple similar reviews to gain some insight into the evaluation quality. Second, the search was

limited to the last 10 years because of a rapid change in lung cancer treatment during recent years and to therefore make results comparable. Applying a longer search period could have resulted in the inclusion of more studies. Third, we searched PubMed and Scopus and included studies in English. Including more databases could have provided more inclusions. In addition, including all languages would have extended our results, as we found a few non-English studies. Finally, this review does have a risk of bias, as firstly, not all health economic evaluations performed might have been published, especially when results show an intervention to be unfavourable.

5 Conclusion

With limited care resources and the increasing technical capabilities to detect multiple different diseases on a single CT scan, exploring the potential benefits of multi-disease screening strategies is increasingly valuable. This directly applies to LDCT given its low cost, low radiation, non-invasive nature and broad range of applications. However, this review shows that health economic evidence for multi-disease screening using CT does not yet exist. Further research on multi-disease screening using LDCT should focus on gathering additional clinical evidence, only then, estimating the health economic impact of multi-disease screening will be feasible. In such an analysis, it is important to consider the complexity of competing risks and heterogeneity of diseases within the target population. In particular, it would also be important to investigate how the optimal target screening population may shift when moving from lung cancer screening to multi-disease screening.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s40273-022-01238-3>.

Author contributions CMB conducted the systematic review and wrote the first draft of the paper. MJOW performed a sample of the abstract screening and the full-text screening as the second reviewer. HK acted as third reviewer by resolving conflicts regarding reviewing after both screening rounds. MJI, RV and HK advised on the goal and implementation of the review and drawing conclusions from the results. All authors reviewed and contributed to the manuscript.

Declarations

Consent to participate No consent was obtained, as there were no participants in this study.

Consent to publish No human research participants were included in this study; therefore, no consent to publish was obtained.

Data availability The data gathered and analysed in this study are included in the article as well as the supplementary materials.

Funding This study is funded by The Netherlands Organisation for Health Research and Development (ZonMw) (IMDI program, dossier number: 10-10400-98-008, B3Care project). The funder had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript. The University of Twente funded the open access publication of this article.

Conflict of interest R. Vliegthart is supported by an institutional research grant from Siemens Healthineers and reports speaker's fees from Siemens Healthineers and Bayer. In addition, M.J. IJzerman has held advisory board roles with respect to Illumina, and his institution (University of Melbourne) receives unrestricted research funding from Illumina. H. Koffijberg, C.M. Behr and M.J. Oude Wolcherink declare that they have no conflict of interest.

Author contributions CMB conducted the systematic review and wrote the first draft of the paper. MJOW performed a sample of the abstract screening and the full-text screening as the second reviewer. HK acted as third reviewer by resolving conflicts regarding reviewing after both screening rounds. MJI, RV and HK advised on the goal and implementation of the review and drawing conclusions from the results. All authors reviewed and contributed to the manuscript.

Ethics approval Not applicable.

Code availability Not applicable.

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