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SYSTEMATIC REVIEW

# Health Economic Research Assessing the Value of Early Detection of Cardiovascular Disease: A Systematic Review

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## Abstract

**Introduction** Cardiovascular disease (CVD) is the most prominent cause of death worldwide and has a major impact on healthcare budgets. While early detection strategies may reduce the overall CVD burden through earlier treatment, it is unclear which strategies are (most) efficient.

**Aim** This systematic review reports on the cost effectiveness of recent early detection strategies for CVD in adult populations at risk.

**Methods** PubMed and Scopus were searched to identify scientific articles published between January 2016 and May 2022. The first reviewer screened all articles, a second reviewer independently assessed a random 10% sample of the articles for validation. Discrepancies were solved through discussion, involving a third reviewer if necessary. All costs were converted to 2021 euros. Reporting quality of all studies was assessed using the CHEERS 2022 checklist.

**Results** In total, 49 out of 5552 articles were included for data extraction and assessment of reporting quality, reporting on 48 unique early detection strategies. Early detection of atrial fibrillation in asymptomatic patients was most frequently studied ($n = 15$) followed by abdominal aortic aneurysm ($n = 8$), hypertension ($n = 7$) and predicted 10-year CVD risk ($n = 5$). Overall, 43 strategies (87.8%) were reported as cost effective and 11 (22.5%) CVD-related strategies reported cost reductions. Reporting quality ranged between 25 and 86%.

**Conclusions** Current evidence suggests that early CVD detection strategies are predominantly cost effective and may reduce CVD-related costs compared with no early detection. However, the lack of standardisation complicates the comparison of cost-effectiveness outcomes between studies. Real-world cost effectiveness of early CVD detection strategies will depend on the target country and local context.

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**Key Points for Decision Makers**

Current evidence suggests that early CVD detection strategies are predominantly cost effective compared with no early detection.

Direct comparison between study outcomes is complicated due to lack of standardisation, but this review is capable of guiding future research towards the most promising early detection strategies.

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## 1 Introduction

The global cardiovascular disease (CVD) burden has been steadily increasing over time with prevalence almost doubling between 1990 and 2019 [1]. Consequently, CVD has become the most prominent cause of death and led to 17.9 million deaths and 365.8 million disability-adjusted life years (DALYs) worldwide in 2017 [2, 3].

The main challenge in reducing the CVD burden is that progression is often unnoticed as CVD is typically asymptomatic in its early stages. Moreover, when symptoms become apparent in later stages, this is often in the form of life-threatening events, such as acute myocardial infarction and ischaemic stroke. Despite recent advances in CVD treatment, acute care remains very expensive and cannot always prevent premature death or (permanent) disability

reducing quality of life. With its high prevalence and high treatment costs following events, CVD puts major pressure on constrained healthcare budgets [4]. In 2017 alone, the cost of CVD in the European Union was 210 billion Euros, of which 111 billion Euros were attributed to direct healthcare costs, such as diagnostic tests and treatment, 54 billion Euros were attributed to productivity losses and 45 billion Euros to informal care [5].

Previous studies have argued that the CVD burden may be reduced more efficiently through preventive strategies than curative strategies [2, 6–8]. Preventive strategies may rely on screening for CVD risk factors or early detection of CVD in asymptomatic individuals to identify individuals who could benefit from preventive medication, such as anti-hypertensive drugs and statins, or lifestyle changes [9]. Early treatment of these individuals at high risk of CVD may prevent the occurrence of life-threatening cardiovascular events and hospital admissions, resulting in potential health benefits and reduced CVD costs.

To assess the balance between the health benefits of early detection strategies and their costs, health economic evaluations have become increasingly important [10]. It is essential for such analyses to estimate both short-term and long-term health effects and costs, as the time between preventive interventions, initiated after early detection, and the resulting future health benefits may be considerable. Clinical trials are suitable to determine short-term outcomes (e.g. occurring within 1–5 years), but only some can be used to determine long-term outcomes, due to time and budget constraints. Consequently, the long-term health and economic impact of early detection strategies are increasingly evaluated by using simulation models. Simulation models are particularly valuable in this context since they allow the estimation of unobserved long-term health outcomes and costs by extrapolating observed intermediate outcomes, such as the yield of early detection strategies. However, choices and assumptions made during modelling may influence health economic outcomes [11]. Therefore, reported outcomes can only be interpreted in light of the choices and assumptions underlying the model and analysis.

Currently, it is unknown which early detection strategies for (risk factors of) CVD are (most) efficient, as systematic reviews concerning the cost effectiveness of such strategies are scarce. To our knowledge, only one systematic review including publications from 2005 to 2015 reported on both the health and economic impact of screening strategies for cardiometabolic diseases [12]. This review showed large heterogeneity in study objectives, country setting, comparators, methodology, outcomes, and screening programmes between studies and between healthcare systems in different countries. Consequently, the authors were unable to make uniform policy recommendations. Moreover, evidence on screening for CVD was limited, as only three out of the 17 included studies focussed explicitly on CVD. Even though specific (cost) outcomes cannot be directly generalised to other countries, a review on different early detection strategies can be valuable to guide future country-specific research towards most the promising strategies, as (new) early detection strategies are identified and health outcomes on different populations are reported. This study aims to systematically review recent health economic evaluations assessing the cost effectiveness of recent early detection strategies targeting CVD in adult populations without prior CVD diagnosis and at risk of developing CVD.

## 2 Methods

### 2.1 Literature Search

A literature search was performed in the online databases PubMed and Scopus. The search strategy included a broad range of early detection strategies for CVD (search queries can be found in Electronic Supplementary Material [ESM] 1). Early detection strategies were defined as strategies aimed at screening for risk factors of CVD or the early detection of CVD in asymptomatic individuals without a previous cardiovascular diagnosis. Given the recent increase in interest in early CVD detection and continuing where the review mentioned in the introduction [12] stopped, only articles published from 1 January 2016 until 30 April 2022 were included. This systematic review (CRD42022321585 in the International Prospective Registry of Ongoing Systematic Reviews) was structured according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (ESM 2) [13].

Covidence software was used for screening articles identified through the search and for data extraction (version 2819 47a0a5d6, Veritas Health Innovation, Australia) [14].

The following inclusion criteria were applied:

1. the study was healthcare-related;
2. the targeted disease was a CVD, defined as diseases within the vascular bed or cardiac area;
3. a full health economic evaluation was performed (i.e. comparing costs and health outcomes of multiple strategies);
4. an early detection strategy was evaluated, defined as a strategy aimed at screening for risk factors for CVD or early detection of CVD in asymptomatic individuals with subsequent appropriate treatment in identified individuals.

The following exclusion criteria were applied:

1. the study focused on animal testing;
2. the target individuals for the early detection strategy were < 18 years old, as populations < 18 years are defined as paediatric care and the majority of CVD events occur in adults;
3. the study focused on secondary prevention, defined as early detection strategies focusing on patients with a prior cardiovascular diagnosis;
4. the study used a time horizon < 1 year.

Assessment of eligibility was performed by one author (MOW), with a second author (CB) screening a random sample of 10% of the title and abstracts and another 10% of the full texts for validation purposes. Discrepancies regarding the inclusion of studies between MOW and CB were discussed and resolved through discussion with a third author (HK).

## 2.2 Data Extraction

Data extraction was performed by one author (MOW). The extracted data were categorised into three sections: general study information and PICOTS (Patient Population, Intervention, Comparator, Outcome, Time, Setting), methodology and outcomes.

### 2.2.1 General Information and PICOTS

The general study information included first author, country in which the study was conducted (if not explicitly mentioned, the country affiliation of the first author was used as proxy), and year of publication. The PICOTS section consisted of mean age and standard deviation (SD) of target population, sex (% female), intervention, comparator, outcome, time horizon, (clinical) setting where the early detection strategy was initiated, and perspective (in case of multiple applied perspectives, the broadest perspective was reported).

### 2.2.2 Methodology

The methodology included the type of early detection strategy (screening for risk factors or early diagnosis of CVD), subsequent management of high-risk individuals or asymptomatic patients, type of included costs, currency, type of health economic analysis, discount rate(s), willingness-to-pay (WTP) threshold, description of different variations on initial strategy assessed (if any), subgroup analyses (if any) and type of study (trial-based or model-based). For trial-based health economic evaluations, additional information regarding study design, inclusion start and end date, duration of follow-up, and method for uncertainty analysis was extracted. For model-based health economic evaluations, information on the type of model, cycle length (for discrete-time models), (time-dependent) estimation of CVD risk based on population characteristics, whether a deterministic sensitivity analysis was performed and whether a probabilistic analysis was performed was extracted. Finally, any methods for (model) validation described were extracted.

### 2.2.3 Outcomes

Regarding results, the following items were extracted: total and incremental costs of the early detection strategy and comparator per person, type of reported health outcomes, total and incremental health outcomes for the early detection strategy and comparator, the incremental cost-effectiveness ratio (ICER) of the base-case analysis, the probability of the (optimal) early detection strategy being cost effective at the applied WTP threshold, and the reported conclusion on cost effectiveness. The following items could also be estimated based on information in the text, tables or figures: total and incremental costs of the early detection strategy and comparator per person, total and incremental health outcomes for the early detection strategy and comparator, the ICER of the base-case analysis, and the probability of the (optimal) early detection strategy being cost effective at the applied WTP threshold. All costs were, if necessary, first converted to Euros using historical exchange rates using OECD data [15] and subsequently indexed to 2021 Euros using Dutch consumer price indices [16]. In case multiple early detection strategies were compared within the same study, the best strategy was described, that is, the strategy providing the highest health benefits with an ICER still below the reported WTP threshold. Converted incremental costs and quality-adjusted life-years were plotted in an incremental cost-effectiveness plane for study comparison. As different WTP thresholds were applied in different countries over the world, all outcomes were also subsequently compared with the Dutch WTP threshold. All results were presented per targeted disease.

## 2.3 Reporting Quality

The 2022 CHEERS checklist was applied to assess the reporting quality of all included articles according to 28 items [17]. An item could receive a score of 0 (insufficient) or 1 (sufficient) for each item. Subsequently, all points were aggregated and divided by the maximum points that could be received (28) to determine the quality score. A score of 85% or higher was considered high quality, between 60% and 85% medium quality, and < 60% as low quality. The reporting quality was assessed over time and per item.

## 3 Results

### 3.1 Screening

Of the 4994 unique articles that were identified in PubMed and Scopus after deduplication, 50 articles were considered for data extraction, as shown in the PRISMA flowchart (Fig. 1). As two included articles reported on the same study in different forms (i.e. one as a journal article [18] and one as a report [19]), the journal article was excluded from data extraction. Finally, two articles studied the impact of the same early detection strategy in different contexts, presumably using the same health economic simulation model [20, 21], resulting in 48 unique early detection strategies included for data extraction. Detailed information on screening can be found in ESM 3.

### 3.2 General Characteristics

The general characteristics of the included articles are shown in Table 1 per targeted disease. The country perspectives most often used were the United States in nine articles (18.4%), Sweden in six articles (12.2%), United Kingdom in six articles (12.2%), and the Netherlands in five articles (10.2%). Only three articles (6.1%) focussed on low- and middle-income countries, namely Nigeria [22, 23] and Vietnam [24]. One study [20] compared the cost effectiveness of an early detection strategy in multiple European countries including Serbia, which is considered a middle-income country. More than half (55.1%) of the studies were funded by non-profit organisations. Ten out of 49 articles (20.4%) reported funding from industry. A quarter of all articles (24.5%) did not report any funding (ESM 4). The target populations ranged from samples of the general population to specific patient groups, such as patients with diabetes mellitus type 2 and autosomal dominant polycystic kidney disease. Most studies compared an early detection strategy with no early detection ($n = 41$, 83.7%). The type of early detection strategies varied substantially between studies from CVD risk prediction tools to identify high-risk individuals to ultrasound scans and computed tomography-based calcium scoring to identify aneurysms and coronary artery disease in asymptomatic individuals. Time horizons ranged from 10 years to lifetime. Out of 49, 34 articles (69.4%) focussed on early detection of CVD in asymptomatic patients, whereas the other 15 articles (30.6%) described screening for CVD risk factors. Early detection of atrial fibrillation in asymptomatic patients was most frequently assessed (30.6%), followed by abdominal aortic aneurysm (18.4%), hypertension (14.3%), and 10-year CVD risk based on Framingham or SCORE risk prediction models (12.2%).

### 3.3 Health Economic Methodology

Methodological characteristics of the health economic evaluations are described in Table 2 per targeted disease. Costs were discounted between 1.5% and 5%, whereas health effects were discounted between 0 and 5%. All studies used simulation modelling to perform the health economic analysis. Markov cohort state transition models (STMs) were used most often, in 27 articles (55.1%), followed by the combination of a decision tree and Markov cohort STM ($n = 11$, 22.4%), microsimulation ($n = 5$, 10.2%), discrete event simulation ($n = 3$, 6.1%), and a decision tree ($n = 1$, 2.0%). Two studies did not report which model type they used [25, 26]. Real-world data from observational studies, registries and national databases were included to inform disease incidence in 18 articles (36.7%), mortality in 30 articles (61.2%), treatment effectiveness in seven articles (14.3%), utility in five articles (10.2%), and resource use and costs in 24 articles (49%) (ESM 5). Overall, 38 studies (77.6%) included a deterministic sensitivity analysis, 33 studies (67.3%) included a probabilistic sensitivity analysis and 26 (53.1%) included both. Finally, only 13 articles (26.5%) reported on (types of) model validation applied (ESM 5).

### 3.4 Outcomes

The outcomes of all health economic evaluations are summarised in Table 3 per targeted disease. The majority of studies ($n = 47$, 95.9%) reported quality-adjusted life-years (QALYs) as the primary health outcome. One article (2.0%) [23] reported disability-adjusted life-years (DALYs) as the main health outcome and one article (2.0%) [25] reported CVD events as the main health outcome. All studies considered direct healthcare costs (i.e. costs of the early detection strategy plus potential events) during the time horizon. Additionally, four studies included costs related to productivity loss and four articles included costs for patients and family. Finally, two studies reported costs per life-year gained. Total costs per person for both the intervention and usual care strategy were reported in 34 articles (69.4%), ranging from €69 to €373,884 for the intervention strategy and €42 to €317,074 for the control strategy. Incremental costs were reported or could be calculated based on total costs in 43 articles (87.8%) and ranged from −€127,266 to €2810 per person. Similarly, average QALYs per person for the intervention and usual care strategy were reported or could be calculated in 30 studies (61.2%) and ranged from 5.96 to 27.41 in the intervention strategy and from 5.95 to 27.35 in the usual care strategy. Incremental QALYs were reported or could be calculated in 40 articles (83.7%) and ranged from 0.00 to 2.87. All outcomes of articles of both incremental costs and incremental health effects were reported or could be calculated are shown in Fig. 2. In total, 47 studies

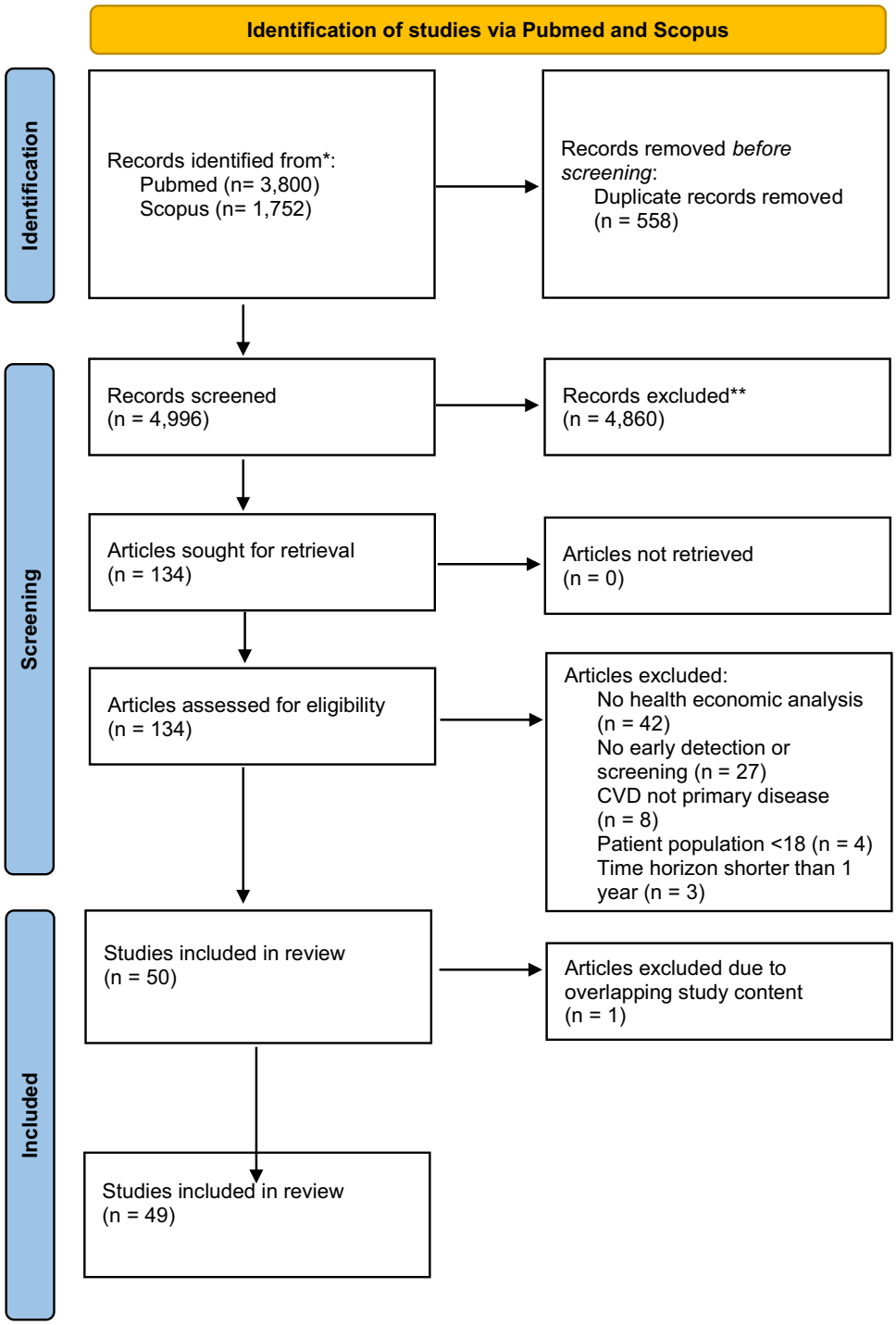


**Fig. 1** 2020 PRISMA flow chart showing the reviewing process

reported ICERs (i.e. costs per QALY gained), ranging from dominance to about €340,000 per QALY gained. Converted WTP thresholds ranged from €1808 to €99,364. In total, 43 out of 49 unique early detection strategies (87.8%) were reported to be cost effective (considering only the best early detection strategy reported per article in case multiple strategies were reported) and 11 articles (22.5%) reported their early detection strategy to be dominant over the comparator considering the applied time horizon. Considering the four most targeted diseases, four out of 15 early detection strategies focussing on atrial fibrillation were dominant, none out of eight early detection strategies focussing on abdominal aortic aneurysm were dominant, one out of seven early detection strategies focussing on hypertension were dominant, and four out of six early detection strategies focussing on 10-year CVD risk were dominant. When comparing the

**Table 1** General characteristics of included articles

| Publication | Country | Patient population[b] | Intervention | Comparator | Primary outcome | Time horizon | Perspective |
|---|---|---|---|---|---|---|---|
| *Atrial fibrillation* | | | | | | | |
| Aronsson et al., 2017 [40] | Sweden | General population aged 55 y | Handheld ECG | No early detection | Cost per QALY | Lifetime | Health care perspective |
| Birkemeyer et al., 2020 [21] | Germany | Population aged 65–85 y | mHealth plethysmography | No early detection | Cost per QALY | Lifetime | Health insurer perspective |
| Giebel, 2020 [41] | Germany | Individuals categorised per $CHA_2DS_2$-VASc risk score (from 1 to 9) | Photoplethysmography with AI | No early detection[a] | Cost per event prevented | 10 y | Health insurer perspective |
| Hill et al., 2020 [42] | UK | Population aged ≥ 50 y | Prediction algorithm | Opportunistic screening | Cost per QALY | Lifetime | NHS perspective |
| Jacobs et al., 2018 [22] | Netherlands | General population aged ≥ 65 y | Single-lead ECG | No early detection | Cost per QALY | Lifetime | Societal perspective |
| Jacobs et al., 2021 [43] | Nigeria | General population aged ≥ 55 y | Single-lead ECG | No early detection | Cost per QALY | Lifetime | Health care perspective |
| McIntyre et al., 2020 [44] | Canada | General population aged ≥ 80 y | 30-day ECG monitoring | No early detection | Cost per QALY | Lifetime | Canadian payer perspective |
| Moran et al., 2016 [45] | Ireland | Population aged ≥ 65 y | Pulse palpation | No early detection | Cost per QALY | 25 y | Societal perspective |
| Oguz et al., 2020 [46] | USA | General population aged ≥ 75 y | 12-lead ECG | No early detection | Cost per QALY | Lifetime | Health care perspective |
| Orchard et al., 2020 [26] | Australia | Population aged ≥ 65 y | eHealth single-lead ECG | No early detection | Cost per QALY | 10 y | Health insurer perspective |
| Proietti et al., 2019 [47] | Belgium | General population aged ≥ 18 y | Handheld single-lead ECG | No early detection | Cost per QALY | 40 y | NR |
| Schnabel et al., 2022 [48] | Germany | General population aged 65–74 y | 12-lead ECG | No early detection[a] | Cost per QALY | Lifetime | NR |
| Sciera et al., 2022 [49] | Denmark | General population aged ≥ 65 y | Pulse palpation | No early detection | Cost per QALY | 19 y | Societal perspective |
| Tarride et al., 2018 [50] | Canada | Population aged ≥ 65 y | Pulse check | No early detection | Cost per QALY | Lifetime | Health care perspective |
| Wahler et al., 2022 [20] | Switzerland; UK; Netherlands; Greece; Poland; Serbia | Population aged 65–85 y | Preventicus Heartbeats medical app | No early detection | Cost per QALY | Lifetime | Health insurer perspective |
| *Abdominal aortic aneurysm* | | | | | | | |
| Fite et al., 2021 [51] | Spain | Population aged 65 y | Ultrasound assessment | No early detection | Cost per QALY | NR | NR |
| Hager et al., 2017 [52] | Sweden | Men in general population aged 65 y | Ultrasound assessment | No early detection | Cost per QALY | Lifetime | Health care perspective |
| Hultgren et al., 2019 [53] | Sweden | Asymptomatic relatives of AAA patients | Ultrasound assessment | No early detection | Cost per QALY | Lifetime | Health care perspective |
| Nair et al., 2019 [54] | New Zealand | Men in general population aged 65 y | Ultrasound assessment | No early detection | Cost per QALY | 30 y | Health care perspective |

**Table 1** (continued)

| Publication | Country | Patient population[b] | Intervention | Comparator | Primary outcome | Time horizon | Perspective |
|---|---|---|---|---|---|---|---|
| Sweeting et al., 2021 [55] | UK | Population aged ≥ 65 y | Ultrasound assessment | No early detection | Cost per QALY | 30 y | NHS perspective |
| Thompson et al., 2018 [19] | UK | Females in general population aged 65 y | Ultrasound assessment | No early detection | Cost per QALY | 30 y | NHS perspective |
| Wanhainen et al., 2016 [56] | Sweden | Men in general population aged 65 y | Ultrasound assessment | No early detection | Cost per QALY | Lifetime | Health care perspective |
| Zarrouk et al. 2016 [29] | Sweden | Men in general population aged 65 y | Ultrasound assessment | No early detection | Cost per QALY | 35 y | NR |
| *Hypertension* | | | | | | | |
| Beyhaghi and Viera, 2019 [57] | USA | General population aged ≥ 21 y | Blood pressure screening | Clinical blood pressure measurement | Cost per QALY | Lifetime | Health care perspective |
| Dehmer et al., 2017 [58] | USA | General population aged 18 y | Aspirin counselling; cholesterol screening; Hypertension screening | No early detection | Cost per QALY | Lifetime | Societal perspective |
| Lee et al., 2021 [59] | South Korea | General population aged ≥ 40 y | Blood pressure screening | No early detection | Cost per QALY | Lifetime | Societal perspective |
| Monahan et al., 2018 [31] | UK | Population aged 40–75 y | Ambulatory blood pressure screening | Current blood pressure screening | Cost per QALY | Lifetime | NHS perspective |
| Nguyen et al., 2016 [24] | Vietnam | General population aged 35–64 y | Blood pressure screening | No early detection | Cost per QALY | Lifetime | Health care perspective |
| Rosendaal et al., 2016 [23] | Nigeria | General population aged 30–79 y | Blood pressure screening | No early detection | Cost per DALY averted | 10 y | Health care perspective |
| Stol et al., 2021 [32] | Netherlands | General population aged 45–70 y | Risk assessment questionnaire | No early detection | Cost per QALY | 60 y | Health care perspective |
| *10-year CVD risk* | | | | | | | |
| Hynninen et al., 2019 [60] | Finland | General population aged ≥ 45 y | Combination of risk factor testing and genetic testing | No early detection | Cost per QALY | 10 y | Health care perspective |
| Kariuki et al., 2018 [25] | USA | African Americans aged 45–64 y | Non-lab Framingham risk assessment | Lab-based Framingham strategy | Cost per event prevented | 12 y | NR |
| Kievit et al., 2017 [61] | Netherlands | Patients with rheumatoid arthritis aged 55 y | SCORE risk assessment | No early detection | Cost per QALY | 10 y | Health care perspective |
| Kypridemos et al., 2018 [30] | UK | General population aged 30–84 y | NHS Health Check | No early detection | Cost per QALY | 23 y | Health care perspective |
| Lagerweij et al., 2020 [62] | Netherlands | Women aged 30 y with pre-eclampsia | Framingham risk assessment | No early detection | Cost per QALY | Lifetime | Health care perspective |
| Smith et al., 2019 [63] | USA | Men in general population aged 52 y | OSCAR CVD risk prediction tool | No early detection | Cost per QALY | 30 y | Societal perspective |

**Table 1** (continued)

| Publication | Country | Patient population[b] | Intervention | Comparator | Primary outcome | Time horizon | Perspective |
|---|---|---|---|---|---|---|---|
| *Coronary artery disease* | | | | | | | |
| van Kempen et al., 2016 [64] | USA | General population aged ≥ 40 y | CT coronary calcium scoring | No early detection | Cost per QALY | Lifetime | Societal perspective |
| Venkataraman et al., 2021 [65] | Australia | Asymptomatic relatives aged 40–70 y with high 5-year CVD risk | CT coronary calcium scoring | Traditional risk factor control[b] | Cost per QALY | 15 y | Health care perspective |
| Ying et al., 2020 [36] | Australia | Kidney transplant candidates aged 18–69 y | No prevention after being placed on waitlist for kidney transplant | Periodical angiogram assessment | Cost per QALY | Lifetime | Health care perspective |
| *Intracranial aneurysm* | | | | | | | |
| Flahault et al., 2018 [66] | France | Patients with autosomal dominant polycystic kidney disease aged 20 y | Magnetic resonance angiography | No early detection | Cost per QALY | Lifetime | NR |
| Malhotra et al., 2019 [39] | USA | Patients with autosomal dominant polycystic kidney disease | Magnetic resonance angiography | No early detection | Cost per QALY | Lifetime | Societal perspective |
| *Peripheral artery disease* | | | | | | | |
| Itoga et al., 2018 [67] | USA | General population aged 65 y | Ankle brachial index screening | No early detection | Cost per QALY | 35 y | Health care perspective |
| Lindholt and Søgaard, 2021 [68] | Denmark | Men aged 65 y | Ankle brachial index and systolic blood pressure | No early detection | Cost per QALY | Lifetime | Health care perspective |
| *Bicuspid valve stenosis* | | | | | | | |
| Tessler et al., 2021 [69] | Israel | Relatives aged 30 y on average | Echocardiography | No early detection | Cost per QALY | Lifetime | Health care perspective |
| *Corotid artery stenosis* | | | | | | | |
| Högberg et al., 2018 [70] | Sweden | Men in general population aged 65 y | Ultrasound assessment | No early detection | Cost per QALY | Lifetime | Health care perspective |
| *Dilated cardiomyopathy* | | | | | | | |
| Catchpool et al., 2019 [28] | Australia | Asymptomatic relatives of dilated cardiomyopathy patients | Genetic cascade testing | Periodical surveillance | Cost per QALY | Lifetime | Health care perspective |
| *Heart failure* | | | | | | | |
| van Giessen et al., 2016 [71] | Netherlands | Patients with type 2 diabetes aged ≥ 60 y | Multiple tests including PE, ECG, and echocardiography | No early detection | Cost per QALY | Lifetime | Health care perspective |
| *Left ventricular disfunction* | | | | | | | |
| Tseng et al., 2021 [72] | USA | Population aged 65 y | ECG with AI | No early detection | Cost per QALY | Lifetime | Health care perspective |

**Table 1** (continued)

| Publication | Country | Patient population[b] | Intervention | Comparator | Primary outcome | Time horizon | Perspective |
|---|---|---|---|---|---|---|---|
| *Overall CVD* | | | | | | | |
| Crossan et al., 2017 [73] | England | Population of 30–74 y | Risk-based health check | Opportunistic assessment | Cost per QALY | Lifetime | NHS perspective |

Parameters were directly extracted from the studies

*AAA* abdominal aortic aneurysm, *AF* atrial fibrillation, *AI* artificial intelligence, *CAD* coronary artery disease, $CHA_2DS_2$-*VASc* Congestive Heart Failure, Hypertension, Age (≥ 75 years), Diabetes, Stroke/Transient Ischemic Attack, Vascular Disease, Sex (Female), *CT* computed tomography, *CVD* cardiovascular disease, *ECG* electrocardiogram, *NHS* National Health Service, *NR* not reported, *OSCAR* OlmeSartan and Calcium Antagonists Randomized trial, *PAD* peripheral artery disease, *PE* physical examination, *QALY* quality-adjusted life-year, *UK* United Kingdom, *USA* United States of America, *y* years

[a]Estimated outcomes that were not directly reported, but could be derived from text, tables or figures

[b]Whenever it was clearly reported that studies looked at a sample from the general population, it was mentioned in this column as 'general population'. If not explicitly stated, it was described as 'Population'

base-case ICERs of all early detection strategies with the Dutch WTP threshold, which is €20,000 when considering preventive strategies, 36 out of 49 (66.7%) were still deemed cost effective.

### 3.5 Reporting Quality

The reporting quality ranged from 25 to 86% (median = 57%) and scores per article are shown in ESM 5. In total, 26 articles (53.1%) were labelled as low quality, 22 (44.9%) as medium quality, and one (2%) as high quality. To assess the reporting quality of articles over time, the reporting quality of all articles is plotted per year of publication in Fig. 3. No improvement in reporting quality could be seen over the years. Most articles reported on how costs were measured and valued ($n = 46$, 93.9%) and on the effect of uncertainty on outcomes ($n = 46$, 93.9%), as can be seen in Fig. 4. Distributional effects and effects of engagement with patients and stakeholders on the design and outcomes, for example, were only reported in one article (2.0%). On the contrary, the valuation and measurement of costs and the effect of uncertainty were reported in most studies ($n = 46$, 93.9%).

## 4 Discussion

This systematic review identified and assessed 49 unique health economic evaluations that focussed on 48 unique early detection strategies for CVD. Almost all included health economic evaluations were performed from a high-income country perspective. Most evaluations compared early detection strategies with no early detection and simulation modelling was used in all studies to estimate (long-term) health and economic impact. Early detection strategies were predominantly cost effective with approximately a quarter also claiming cost reductions. This suggests that early detection of CVD is likely to be cost effective given the respective WTP thresholds applied. However, this could also be (in part) explained by the fact that studies with a negative outcome may be published less often [27]. No disease-specific early detection strategy appeared to be much more cost effective than others. Moreover, of the four most targeted diseases, 10-year CVD risk prediction showed the most promising results being dominant in 67% of all studies. When comparing the ICERs with the Dutch WTP threshold, two-thirds of the reported ICERs fall below this threshold, indicating that the majority of strategies would be cost effective when consistently applying this WTP threshold. Compared with the previous systematic review mentioned in the introduction [12], substantially more studies focussing on early detection of CVD were identified (49 vs 5). Both reviews showed that reported ICERs varied substantially. However, 11 studies (22.4%) in this review reported the

**Table 2** Methodology of health economic evaluation

| Publication | Currency | Annual discount rate for costs (%) | Annual discount rate for health effects (%) | Type of model | Cycle length (in months)[a] | Deterministic sensitivity analysis performed? | Probabilistic analysis performed? |
|---|---|---|---|---|---|---|---|
| *Atrial fibrillation* | | | | | | | |
| Aronsson et al., 2017 [40] | 2016 EUR | 3 | 3 | Markov | 12 | Yes | Yes |
| Birkemeyer et al., 2020 [21] | EUR[b] | 3 | 3 | Markov | NR | Yes | Yes |
| Giebel, 2020 [41] | EUR[b] | 3 | 3 | Markov | 12 | No | No |
| Hill et al., 2020 [42] | 2017 GBP | 3.5 | 3.5 | DT-Markov | NR | Yes | No |
| Jacobs et al., 2018 [22] | EUR[b] | 4 | 1.5 | DT-Markov | 3 | Yes | Yes |
| Jacobs et al., 2021 [43] | 2018 USD | 4 | 4 | DT-Markov | 6 | Yes | Yes |
| McIntyre et al., 2020 [44] | 2014 USD | 1.5 | 1.5 | Markov | NR | No | Yes |
| Moran et al., 2016 [45] | EUR[b] | 5 | 5 | Markov | 12 | No | Yes |
| Oguz et al., 2020 [46] | 2016 USD | 3 | 3 | Markov | 3 | Yes | Yes |
| Orchard et al., 2020 [26] | AUD[b] | 5 | 5 | NR | NR | Yes | No |
| Proietti et al., 2019 [47] | EUR[b] | NR | NR | Markov | NR | No | Yes |
| Schnabel et al., 2022 [48] | 2018 EUR | NR | NR | Markov | 12 | Yes | No |
| Sciera et al., 2022 [49] | 2018 EUR | 4 | NR | DT-Markov | 12 | Yes | No |
| Tarride et al., 2018 [50] | 2017 CAD | 1.5 | 1.5 | Markov | 12[c] | Yes | Yes |
| Wahler et al., 2022 [20] | 2014 EUR | 3 | 3 | Markov | NR | Yes | No |
| *Abdominal aortic aneurysm* | | | | | | | |
| Fite et al., 2021 [51] | EUR[b] | NR | NR | Markov | NR | No | No |
| Hager et al., 2017 [52] | 2013 EUR | 3 | 3 | Markov | 12 | Yes | Yes |
| Hultgren et al., 2019 [53] | 2016 EUR | 3 | 3 | Markov | 12 | Yes | Yes |
| Nair et al., 2019 [54] | 2011 NZD | 3 | 3 | Markov | 3 | Yes | Yes |
| Sweeting et al., 2021 [55] | 2019 GBP | 3.5 | 3.5 | DES | NA | Yes | Yes |
| Thompson et al., 2018 [19] | 2015 GBP | 3.5 | 3.5 | DES | NA | Yes | Yes |
| Wanhainen et al., 2016 [56] | EUR[b] | 3 | 3 | Markov | 12[c] | No | No |
| Zarrouk et al. 2016 [29] | 2014 EUR | 3 | 3 | Markov | 12 | Yes | No |
| *Hypertension* | | | | | | | |
| Beyhaghi and Viera, 2019 [57] | 2017 USD | 3 | 3 | DT-Markov | 12 | Yes | Yes |
| Dehmer et al., 2017 [58] | 2012 USD | 3 | 3 | MS | 12 | Yes | No |
| Lee et al., 2021 [59] | KRW[b] | 5 | 5 | DT-Markov | 12 | Yes | No |
| Monahan et al., 2018 [31] | GBP[b] | 3.5 | 3.5 | Markov | 3 | Yes | Yes |

**Table 2** (continued)

| Publication | Currency | Annual discount rate for costs (%) | Annual discount rate for health effects (%) | Type of model | Cycle length (in months)[a] | Deterministic sensitivity analysis performed? | Probabilistic analysis performed? |
|---|---|---|---|---|---|---|---|
| Nguyen et al., 2016 [24] | 2013 USD | 3 | 0 | DT-Markov | 12 | Yes | Yes |
| Rosendaal et al., 2016 [23] | 2012 USD | 3 | 3 | Markov | 12 | Yes | Yes |
| Stol et al., 2021 [32] | 2014 EUR | 4 | 1.5 | Markov | NR | Yes | No |
| *10-year CVD risk* | | | | | | | |
| Hynninen et al., 2019 [60] | 2015 EUR | 3 | 3 | DT | NA | Yes | Yes |
| Kariuki et al., 2018 [25] | USD[b] | 3 | 3 | NR | NR | No | No |
| Kievit et al., 2017 [61] | 2012 EUR | 4 | 1.5 | Markov | 12 | Yes | Yes |
| Kypridemos et al., 2018 [30] | 2016 GBP | 3.5 | 3.5 | MS | NR | No | Yes |
| Lagerweij et al., 2020 [62] | EUR[b] | 4 | 1.5 | MS | 12 | No | Yes |
| Smith et al., 2019 [63] | 2015 USD | 3 | 3 | Markov | 12 | Yes | No |
| *Coronary artery disease* | | | | | | | |
| van Kempen et al., 2016 [64] | 2014 USD | 3 | 3 | Markov | 12 | Yes | Yes |
| Venkataraman et al., 2021 [65] | 2020 USD | 3 | 3 | MS | 12 | Yes | Yes |
| Ying et al., 2020 [36] | 2016 AUD | 5 | 5 | MS | 12 | Yes | Yes |
| *Intracranial aneurysm* | | | | | | | |
| Flahault et al., 2018 [66] | 2016 EUR | NR | NR | Markov | 12 | No | Yes |
| Malhotra et al., 2019 [39] | 2016 USD | 3 | 3 | DT-Markov | 12[c] | Yes | Yes |
| *Peripheral artery disease* | | | | | | | |
| Itoga et al., 2018 [67] | 2017 USD | 3 | NR | Markov | 1 | Yes | No |
| Lindholt and Søgaard, 2021 [68] | EUR[b] | 3.5 | 3.5 | DT-Markov | 12 | Yes | Yes |
| *Bicuspid valve stenosis* | | | | | | | |
| Tessler et al., 2021 [69] | 2019 EUR | 3 | 3 | DT-Markov | 12[c] | Yes | Yes |
| *Corotid artery stenosis* | | | | | | | |
| Högberg et al., 2018 [70] | 2016 EUR | 3.5 | 3.5 | Markov | 12 | Yes | No |
| *Dilated cardiomyopathy* | | | | | | | |
| Catchpool et al., 2019 [28] | 2018 AUD | 5 | 5 | DT-Markov | 12 | Yes | Yes |
| *Heart failure* | | | | | | | |
| van Giessen et al., 2016 [71] | EUR[b] | 4 | 1.5 | Markov | 3 | No | Yes |
| *Left ventricular disfunction* | | | | | | | |
| Tseng et al., 2021 [72] | 2018 USD | 3 | 3 | DT-Markov | NR | Yes | Yes |

**Table 2** (continued)

| Publication | Currency | Annual discount rate for costs (%) | Annual discount rate for health effects (%) | Type of model | Cycle length (in months)[a] | Deterministic sensitivity analysis performed? | Probabilistic analysis performed? |
|---|---|---|---|---|---|---|---|
| *Overall CVD* | | | | | | | |
| Crossan et al., 2017 [73] | 2015 GBP | 3.5 | 3.5 | DES | NA | Yes | Yes |

Parameters were directly extracted from the studies

*AUD* Australian dollar, *CAD* Canadian dollar, *CEA* cost-effectiveness analysis, *CUA* cost-utility analysis, *CVD* cardiovascular disease, *DES* discrete event simulation, *DT* decision tree, *DT-Markov* combination of decision tree and Markov model, *EUR* euro, *GBP* Great British Pound, *HEE* health economic evaluation, *KRW* Korean Won, *Markov* Markov cohort state transition model, *MS* microsimulation (patient-level state transition model), *NA* not applicable, *NR* not reported, *NZD* New Zealand dollar, *USD* United States dollar

[a]Only applicable to discrete time models

[b]Year of the currency used was not reported. The year in which the article was published was used as proxy

[c]Values were not directly reported, but could be derived from the article or supplementary materials

early detection strategy to be dominant over the comparator, whereas the earlier review did not mention any early detection strategy to be dominant.

The median reporting quality of studies according to the CHEERS 2022 was 57% (ranging from 25 to 86%) and quality was considered high in only one health economic evaluation. Whereas reporting quality varied per year, it seems to remain consistent over time. No conclusions on the studies from 2022 can be made yet, as only two relevant articles were published in the included months (January 1–April 30). When investigating the items individually, it was apparent that several specific items consistently scored poorly. For example, engagement with patients and stakeholders and the effect thereof were rarely reported. Only one study created a patient committee that was involved in the design of the study [19], whereas two studies involved a multidisciplinary team with clinical experts in the development of the simulation model [28, 29]. Furthermore, distributional effects and health (in)equality were only mentioned in one study [30]. Only two studies referred to a health economic evaluation plan [31, 32]. All the above-mentioned items were added in the latest version of CHEERS in 2022. This may explain why few studies reported these items, as all included studies were published before or at the beginning of 2022. Surprisingly, the items mentioning perspective, time horizon and to a lesser extent discount rate were also scored poorly. Although these choices were mentioned in most articles, the reasons for choosing a certain perspective, time horizon and discount rates were not reported, leading to low scores.

Several findings were striking. Regarding the model type used, the Markov cohort STM was by far the most used simulation model. However, such models may not be most suitable to simulate the long-term impact of early detection strategies for CVD. Limitations of Markov cohort STMs are that they are rather unsuitable to include heterogeneity and have limited flexibility to consider the history of patients [33]. When estimating the occurrence of CVD events, the risk of developing CVD may depend on many different (risk) factors and medical history which may be harder to adequately incorporate in a cohort Markov STM compared with a patient-level simulation model. While a Markov cohort STM may require fewer inputs than patient-level simulation models, a Markov cohort STM may yield comparable results when inputs are carefully assessed and patient-level parameters are appropriately considered and reflected [34]. Justification for the choice of a Markov cohort STM was, however, lacking in most included studies. It can be argued that patient-level models may be more suitable for early detection strategies in particlular, as they are well suited to include heterogeneity, long-term memory, and account for the (long-term) clinical and treatment history of simulated individuals. In addition, current computing power, detailed tutorials and supporting programming code [35] have made the use of patient-level models for standard health economic analyses quite feasible. Still, only eight studies (i.e. 5 microsimulations and 3 discrete event simulations) used a patient-level simulation model.

The aggregated costs per individual deviated substantially between studies, ranging from below 100 Euros to hundreds of thousands of Euros. Multiple causes could (partly) explain the differences in costs. Firstly, the target population ranged from general population samples to samples of specific patient populations. For example, one study only included patients on the waiting list for kidney transplantation [36]. These patients already incur high costs for dialysis regardless of potentially developing CVD, contributing to very high costs per individual. Secondly, the type(s) of costs included varied per study. Whereas some studies only included direct healthcare costs, other studies included productivity losses and costs per life-year gained, that is, the additional healthcare costs an individual makes for living longer, in addition to

**Table 3** Outcomes of health economic evaluations

| Publication[a] | Costs for early detection strategy per person (in 2021 EUR)[b] | Costs for comparator per person (in 2021 EUR)[b] | Incremental costs (in 2021 EUR)[b] | QALYs for early detection strategy per person[a] | QALYs for comparator per person[a] | Incremental QALY[a] | Base case ICER (in 2021 EUR/QALY)[b] | Reported WTP threshold (converted to 2021 EUR)[b] | Probability early detection strategy is cost effective (in %)[a] |
|---|---|---|---|---|---|---|---|---|---|
| *Atrial fibrillation* | | | | | | | | | |
| Aronsson et al., 2017 [40] | NR | NR | 60.96 | NR | NR | 0.00 | 18,046 | 55,019 | NR |
| Birkemeyer et al., 2020 [21] | NR | NR | − 132.25 | 7.92 | 7.91 | 0.02 | Dominant | NR | 100 |
| Giebel, 2020 [41] | 7363 | 6676 | 686.92 | NR | NR | NR | NR | NR | 75 |
| Hill et al., 2020 [42] | 503[c] | 489[c] | 14.09[c] | NR | NR | 0.00 | 6854 | 24,726 | NR |
| Jacobs et al., 2018 [22] | 12,583 | 13,398 | −815.07 | 8.02 | 7.75 | 0.27 | Dominant | 21,344 | 99.8 |
| Jacobs et al., 2021 [43] | NR | NR | 509.80 | NR | NR | 0.41 | 1232 | 1808 | 99.9 |
| McIntyre et al., 2020 [44] | NR | NR | 229.13 | NR | NR | 0.01 | 41,730 | 41,813 | 24 |
| Moran et al., 2016 [45] | 16,080 | 15,987 | 92.43 | 7.82 | 7.82 | 0.00 | 25,313 | 49,517 | 79 |
| Oguz et al., 2020 [46] | 6949 | 6325 | 624.37 | 7.01 | 7.00 | 0.01 | 47,644 | 99,364 | 88 |
| Orchard et al., 2020 [26] | NR | NR | NA | NR | NR | NR | 10,262 | NR | NR |
| Proietti et al., 2019 [47] | 249[c] | 170[c] | 78.81[c] | 8.83 | 8.82 | 0.01 | 6975 | 31,195 | NR |
| Schnabel et al., 2022 [48] | NR | NR | NR | NR | NR | NR | 32,401 | NR | NR |
| Sciera et al., 2022 [49] | 102[c] | 42[c] | 60.19[c] | 7.31[c] | 7.30[c] | 0.01[c] | 10,032 | 23.478 | NR |
| Tarride et al., 2018 [50] | 150 | 159 | 8.68 | 8.74 | 8.74 | 0.00 | Dominant | 37,004 | 63 |
| Wahler et al., 2022 [20] | NR | NR | −€83.19 (CH)<br>−€7.56 (UK)<br>€6.63 (GR)<br>€17.15 (NL)<br>€22.1 (PL)<br>€36.69 (S) | NR | NR | 0.01 (CH)<br>0.01 (UK)<br>0.01 (GR)<br>0.01 (NL)<br>0.02 (PL)<br>0.01 (S) | Dominant (CH)<br>Dominant (UK)<br>€543 (GR)<br>€1698 (NL)<br>€1182 (PL)<br>€2830 (S) | NR | NR |
| *Abdominal aortic aneurysm* | | | | | | | | | |
| Fite et al., 2021 [51] | NR | NR | NR | NR | NR | NR | 13,664 | NR | NR |
| Hager et al., 2017 [52] | 425 | 260 | 164.84 | 10.77 | 10.75 | 0.02 | 7093 | 26,913 | ~100[c] |
| Hultgren et al., 2019 [53] | 680 | 456 | 224.48 | 10.67 | 10.65 | 0.03 | 8436 | 11,004 | 81 |

**Table 3** (continued)

| Publication[a] | Costs for early detection strategy per person (in 2021 EUR)[b] | Costs for comparator per person (in 2021 EUR)[b] | Incremental costs (in 2021 EUR)[b] | QALYs for early detection strategy per person[a] | QALYs for comparator per person[a] | Incremental QALY[a] | Base case ICER (in 2021 EUR/QALY)[b] | Reported WTP threshold (converted to 2021 EUR)[b] | Probability early detection strategy is cost effective (in %)[a] |
|---|---|---|---|---|---|---|---|---|---|
| Nair et al., 2019 [54] | 20,352[c] | 20,257[c] | 94.85 | 9.21 | 9.2 | 0.01 | 5174 | 14,762 | 80 |
| Sweeting et al., 2021 [55] | 314 | 239 | 74.69 | NR | NR | 0.01 | 9816 | 23,719 | 49 |
| Thompson et al., 2018 [19] | 149 | 80 | 68.44 | 8.73 | 8.73 | 0.00 | 34,227 | 30,370 | 42 |
| Wanhainen et al., 2016 [56] | 1389 | 896 | 492.97 | NR | NR | 0.06 | 8550 | NR | NR |
| Zarrouk et al. 2016 [29] | 901 | 713 | 187.69 | 10.93 | 10.92 | 0.01 | 17,447 | 22,211 | NR |
| *Hypertension* | | | | | | | | | |
| Beyhaghi and Viera, 2019 [57] | NR | NR | − 4815.59 | NR | NR | 0.08 | Dominant | 48,031 | 100 |
| Dehmer et al., 2017 [58] | NR | NR | 1091.79 | NR | NR | 0.16[c] | 43,371 | 44,712 | NR |
| Lee et al., 2021 [59] | 24,516[c] | 24,468[c] | 48.01[c] | 18.56[c] | 18.56[c] | 0.00[c] | 14,716 | 22,160 | NR |
| Monahan et al., 2018 [31] | 4084 | 3947 | 137.39 | 18.153 | 18.116 | 0.04 | 3713 | 24,104 | 100 |
| Nguyen et al., 2016 [24] | 242 | 232 | 10.49 | 5.96 | 5.95 | 0.00 | 3599 | 13,412 | 99[c] |
| Rosendaal et al., 2016 [23] | 69 | 54 | 14.76 | NR | NR | NR | 655 | 2452 | 99 |
| Stol et al., 2021 [32] | NR | NR | NR | NR | NR | NR | 339,832 | 22.211 | NR |
| *10-year CVD risk* | | | | | | | | | |
| Hynninen et al., 2019 [60] | 1848 | 1817 | 30.91 | 7.63 | 7.62 | 0.01 | 2361[c] | 55,195 | 100 |
| Kariuki et al., 2018 [25] | 2803 | 3111 | − 307.27[c] | NR | NR | NR | Dominant | NR | NR |
| Kievit et al., 2017 [61] | 2593 | 3870 | − 1214.93 | 6.3 | 6.21 | 0.09 | Dominant | 22,988 | 95[c] |
| Kypridemos et al., 2018 [30] | NR | NR | − 0.23[c] | NR | NR | 0.00 | Dominant | 26,819 | 100 |
| Lagerweij et al., 2020 [62] | 11,871 | 9679 | 2192.19 | 27.41 | 27.35 | 0.06 | 35,933 | 20,536 | 10[c] |
| Smith et al., 2019 [63] | 26,395 | 29,952 | − 3556.74 | 15.53 | 15.37 | 0.16 | Dominant | NR | NR |

**Table 3** (continued)

| Publication[a] | Costs for early detection strategy per person (in 2021 EUR)[b] | Costs for comparator per person (in 2021 EUR)[b] | Incremental costs (in 2021 EUR)[b] | QALYs for early detection strategy per person[a] | QALYs for comparator per person[a] | Incremental QALY[a] | Base case ICER (in 2021 EUR/QALY)[b] | Reported WTP threshold (converted to 2021 EUR)[b] | Probability early detection strategy is cost effective (in %)[a] |
|---|---|---|---|---|---|---|---|---|---|
| *Coronary artery disease* | | | | | | | | | |
| van Kempen et al., 2016 [64] | 13,601 | 12,786 | 814.51 | 14.68 | 14.65 | 0.03 | 27,151 | 41,813 | 45 |
| Venkataraman et al., 2021 [65] | 5540 | 5345 | 130.42 | 9.39 | 9.38 | 0.01 | 13,505 | 44,973 | 91 |
| Ying et al., 2020 [36] | 373,884 | 371,074 | 2810.27[c] | 7.67 | 7.31 | 0.36[c] | 8217 | 36,938 | 94 |
| *Intracranial aneurysm* | | | | | | | | | |
| Flahault et al., 2018 [66] | NR | NR | NR | NR | NR | 1.29[c] | NR | 55,019 | 99 |
| Malhotra et al., 2019 [39] | 19,713 | 146,979 | − 127,265.67[c] | 25.86 | 22.99 | 2.87 | Dominant | 99,364 | ~ 100[c] (vs no prevention) |
| *Peripheral artery disease* | | | | | | | | | |
| Itoga et al., 2018 [67] | 19,407 | 19,115 | 324.69 | 9.65 | 9.65 | 0.00 | 85,263 | 48,031 | NA |
| Lindholt and Søgaard, 2021 [68] | 3974 | 3323 | 650 | 9.53 | 9.48 | 0.05 | 12,397 | NR | NR |
| *Bicuspid valve stenosis* | | | | | | | | | |
| Tessler et al., 2021 [69] | 2433 | 3103 | − 669.66 | 26.8 | 26.5 | 0.3 | Dominant | 45,493 | 83 |
| *Corotid artery stenosis* | | | | | | | | | |
| Högberg et al., 2018 [70] | 9581 | 8322 | 1259.81 | 7.67 | 7.47 | 0.1993 | 6321 | 25,309 | NR |
| *Dilated cardiomyopathy* | | | | | | | | | |
| Catchpool et al., 2019 [28] | 2432 | 2229 | 202.67 | 14.96 | 14.92 | 0.04 | 2094 | 33,778 | 90 |
| *Heart failure* | | | | | | | | | |
| van Giessen et al., 2016 [71] | 8368 | 7477 | 891.31 | 12.48 | 12.35 | 0.13[c] | 6729 | 22,008 | 90 |
| *Left ventricular disfunction* | | | | | | | | | |
| Tseng et al., 2021 [72] | 198,634 | 197,831 | 802.22[c] | 9.53 | 9.52 | 0.02[c] | 47,068 | 90,391 | 93 |
| *Overall CVD* | | | | | | | | | |
| Crossan et al., 2017 [73] | NR | NR | 24.65[c] | NR | NR | 0.00[c] | 2824 | 30,370 | 45.6[c] |

*CH* Switzerland, *CVD* cardiovascular disease, *EUR* euro, *GR* Greece, *ICER* incremental cost-effectiveness ratio, *NA* not applicable, *NL* Netherlands, *NR* not reported, *PL* Poland, *QALY* quality-adjusted life-year, *S* Serbia, *UK* United Kingdom, *WTP* willingness-to-pay threshold

[a]Parameters that were directly extracted from the studies

[b]Parameters that were synthesised by the reviewers after extraction of data

[c]Estimated outcomes that were not directly reported, but could be derived from text, tables or figures

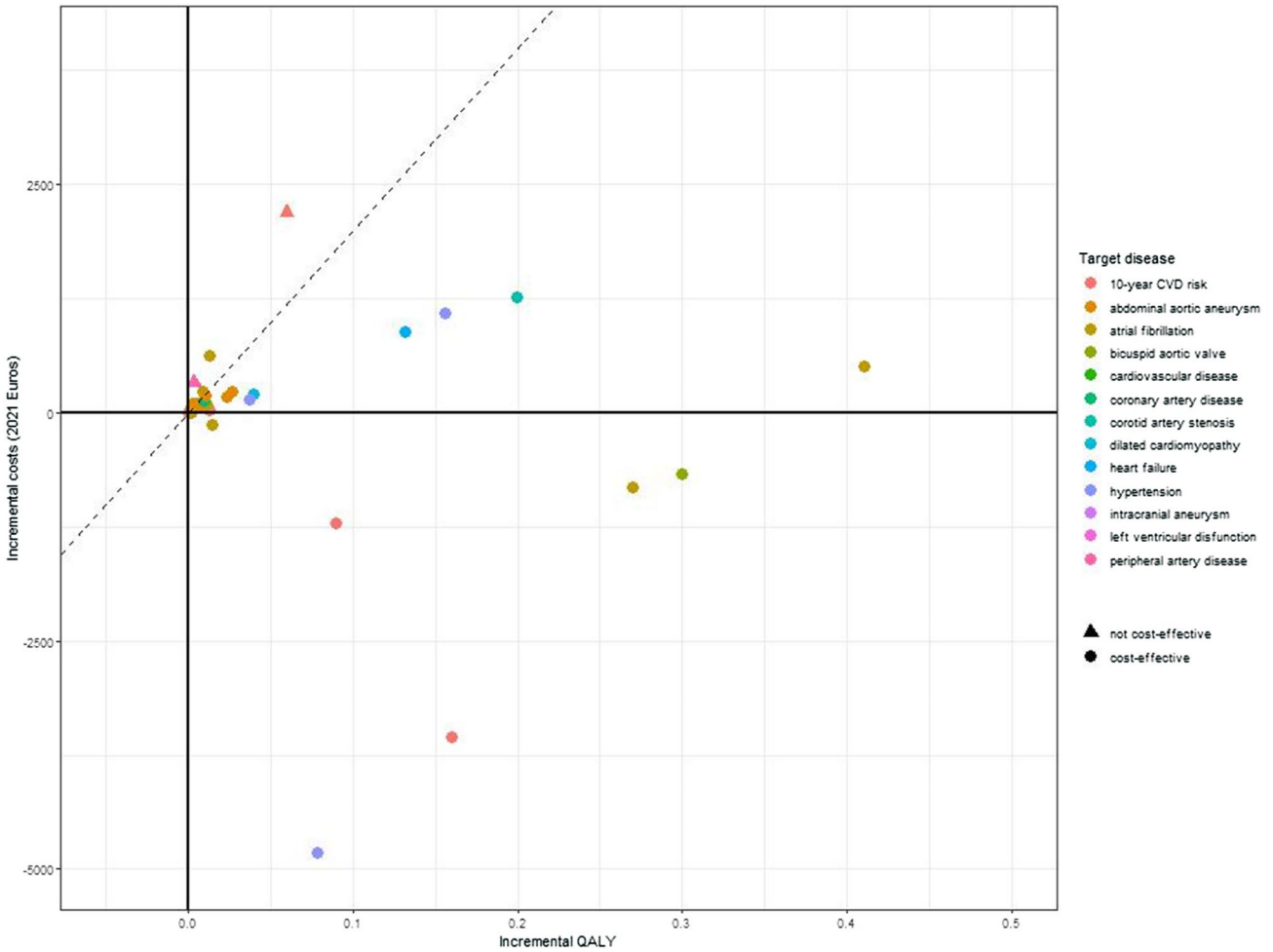


**Fig. 2** Incremental health economic outcomes of all papers reporting both costs and quality-adjusted life-years (QALYs). The colour represents the targeted disease of the early detection strategy and the shape reflects the authors' conclusion. The dashed line represents the Dutch willingness-to-pay threshold of €20,000/QALY. One publication [39] reported both incremental costs and QALYs, but had such large QALY gain (2.87) that it was removed from this figure for visualisation purposes

direct healthcare costs. Thirdly, the time horizon and age of inclusion varied greatly between studies, which may influence total costs and QALYs per individual, as younger simulated individuals typically consume more healthcare resources and collect more QALYs due to longer survival. Fourthly, the costs of early detection strategies varied greatly between studies, depending on the screening method used and the management of individuals after a positive screening result. Finally, medical guidelines and care pathways may differ per country, particularly between low-, middle-, and high-income countries, leading to different healthcare resource use and costs of treatment. However, despite the large and expected variations in (cost) outcomes, our results allow clinicians to identify promising strategies based on conclusions of health economic assessments performed in countries with largely similar health systems. This identification can be based on, for example, combined (health) outcomes, on targeted population, or on the type of early detection strategy.

Generally, age is considered an important risk factor for CVD [37]. However, of the included studies, only 12 reportedly implemented age-dependent risks for developing CVD or developing CVD events, while the remainder used constant age-independent risks (ESM 4). The use of a constant, average CVD risk regardless of age could easily lead to overestimation of disease incidence early in the simulation or underestimation of disease incidence later in the simulation, affecting incremental health effects and the resulting ICER. Furthermore, some studies mentioned that early detection strategies for CVD will lead to cost savings, because future cardiovascular events and associated costs may be avoided, thus improving survival and quality of life. However, living longer due to avoided CVD events also leads to additional healthcare costs, which need to be considered as well [38].

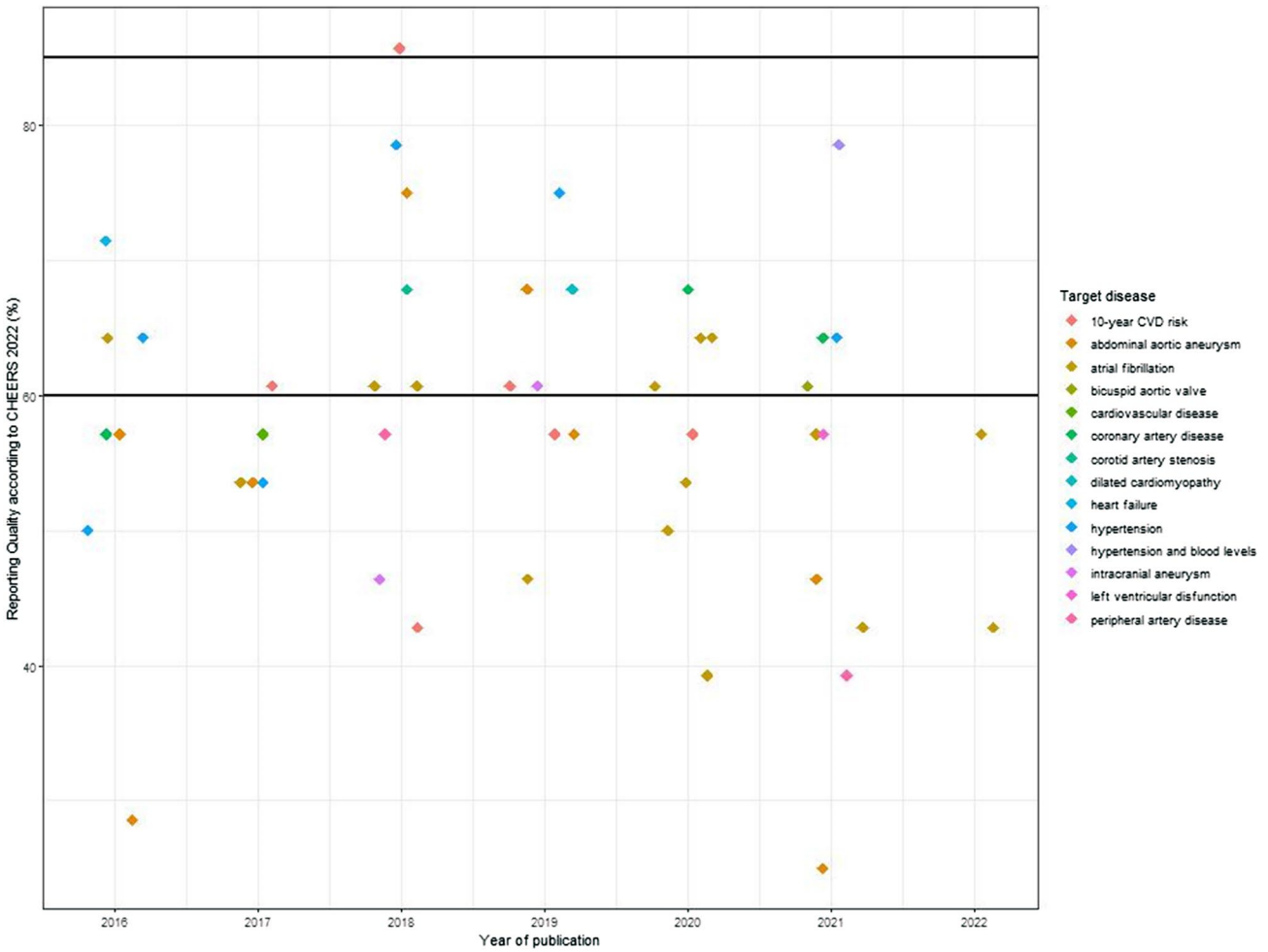


**Fig. 3** Reporting quality of health economic articles over the included time period, i.e. from January 2016 until May 2022. The colours represent the target disease and the horizontal lines separate low, medium, and high quality articles. For visability, some noise was added to the *x*-value

Only two included articles mentioned they included these additional costs in their health economic evaluation. Most reported conclusions that an early detection strategy is cost saving from a health care or societal perspective should therefore be considered with caution and interpreted only in terms of an expected reduction in CVD-related costs. Finally, it was striking that only about a quarter of all studies reported on validation methods of the simulation model (shown in ESM 5), as proper validation is essential for good outcome interpretation.

This review has several strengths and limitations. This is one of the first systematic reviews focussing on both health and economic outcomes of early detection strategies for CVD. Health economic model developers could benefit from learning about existing models and their structure, when developing their own. This may render model development more efficient. CVD is a very complex disease including all diseases to the cardiac area and vascular bed. While likely introducing large heterogeneity to our findings, broad search terms were used to ensure all types of CVD and all known risk factors that increase the risk of developing CVD were included. We chose to exclude studies in which other diseases known to be a risk factor for CVD, such as diabetes mellitus and chronic kidney disease, were targeted, as this complicates determining the specific impact of those strategies on the CVD burden. Therefore, only studies remain that clearly focus on CVD and described the outcomes within that context. One limitation is the exclusion of grey literature. Therefore, policy-related documents discussing health economic evaluations could have been missed. However, such documents are unlikely to (independently) report on a full health economic evaluation. Moreover, data extraction was performed by a single reviewer, which may have led to some inconsistencies. Additionally, this study attempted to compare the health and economic outcomes of different health economic evaluations with many different country perspectives and with varying underlying assumptions and choices. However, health economic outcomes will be

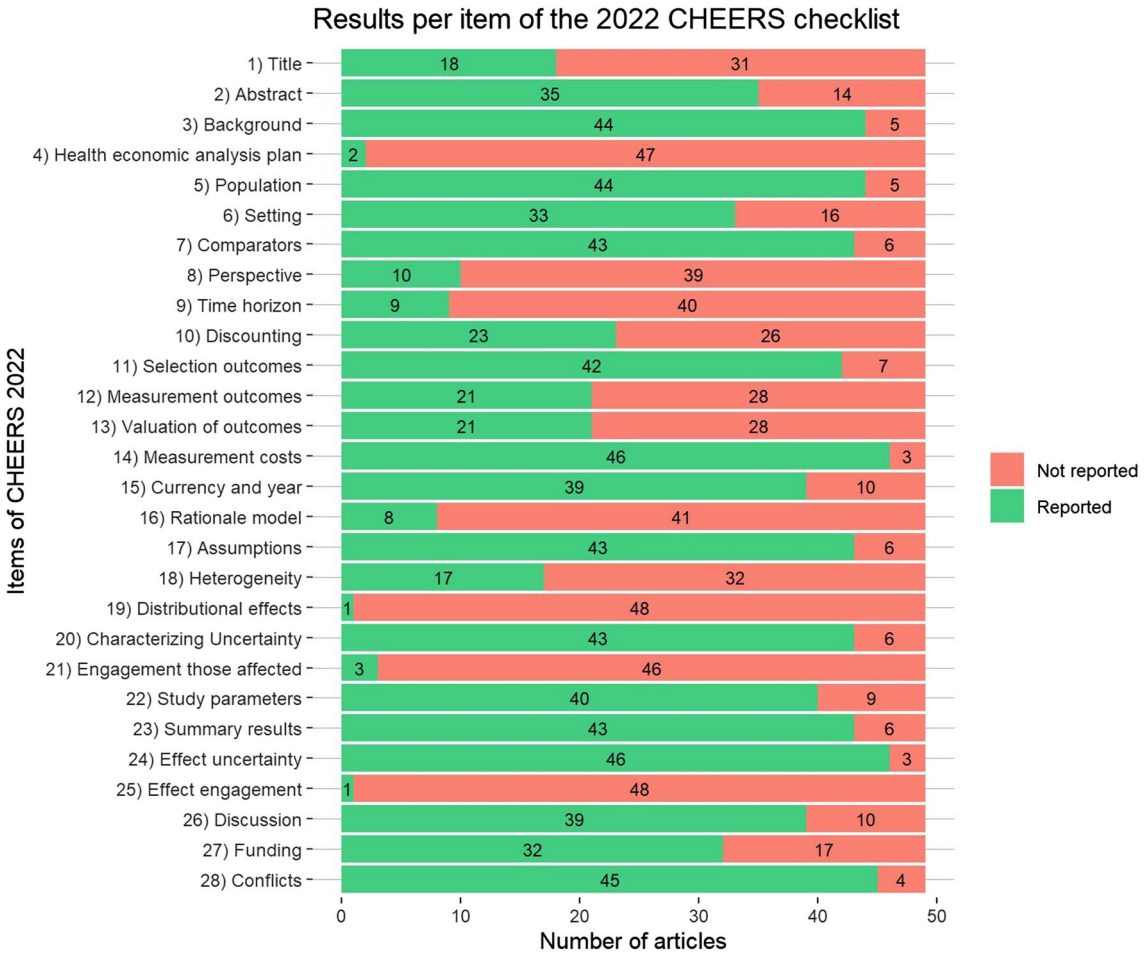


**Fig. 4** Overview of how many articles reported on each item of the 2022 CHEERS checklist

influenced by methodological choices and country perspectives. No correction was applied to address these issues, as no widely accepted correction method is currently available. Converting all costs to 2021 Euros using Dutch consumer price indexes likely affects outcomes, but it is yet unknown how large differences are when using consumer price indexes of other (Euro) countries. However, other consumer price indexes do not impact the cost effectiveness of dominant interventions. Finally, there were no exclusion criteria based on language, but articles without an English abstract could not be found due to the English search strategy.

Many health economic evaluations focussing on the impact of early detection strategies regarding CVD compare early detection strategy with no early detection. While many early detection strategies may be cost effective when compared with no early detection, some strategies will certainly outperform others. Given different methodological choices and country perspectives, including differences in (cost of) usual care, it is challenging to directly compare early detection strategies described in different health economic evaluations. A way to perform such comparison would be to assess the transferability of results from different evaluations to a specific jurisdiction (e.g. Dutch setting). However, performing such systematic comparison was beyond the scope of the current study. Moreover, comparison of different early detection strategies for CVD with consistent methodological choices, in a single validated and accepted simulation model (i.e. a 'reference model') would be valuable to support policymakers with identifying and implementing the most efficient early detection strategy. For instance, uniformising methodological choices concerning the type of model to use, the methods for extrapolating CVD risk and cost categories and health outcomes to consider may contribute to such an endeavour.

## 5 Conclusion

Current evidence suggests that early detection strategies for CVD are predominantly cost effective and may reduce CVD costs compared with no early detection. However, the

lack of standardisation complicates the comparison of cost-effectiveness outcomes between studies. Real-world cost effectiveness of early CVD detection strategies will depend on the target country and local context.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s40273-023-01287-2.

## Declarations

**Conflict of interest** The authors have no competing interests to declare.

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**Author contributions** MJ Oude Wolcherink screened the articles and drafted the first version of the manuscript. CM Behr designed the review and screened a sample of title and abstracts and full-text articles. H Koffijberg was the third reviewer when conflicts during screening arose. CJM Doggen, H Koffijberg, and XLGV Pouwels all performed supervision tasks during the study. All authors reviewed and contributed to the manuscript.

**Data availability statement** All articles can be found in either PubMed or Scopus using the respective search query as shown in electronic supplementary material (ESM) 1. The dataset with screening results are shown in ESM 3. All data obtained from the data extraction are shown in Tables 1, 2, 3 within the manuscript or in ESM 4 and 5. Finally, all outcomes of reporting quality assessment are shown in ESM 6.



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