

WHO HEALTH EVIDENCE NETWORK SYNTHESIS REPORT 71

What is the effectiveness of systematic population-level screening programmes for reducing the burden of cardiovascular diseases?

Christian Ulrich Eriksen | Oxana Rotar | Ulla Toft | Torben Jørgensen



**World Health
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Abstract

Cardiovascular diseases (CVDs) remain the main cause of death in the WHO European Region. This systematic literature review assesses whether systematic screening programmes for CVD risk factors and preclinical CVDs across general populations can lower the CVD burden in society. Based on several high-quality randomized controlled trials with large numbers of participants, the results clearly showed that screening for CVD risk factors has no effect on lowering CVD morbidity and mortality in society. Studies showed that screening for preclinical CVDs slightly reduces mortality and negative outcomes related to abdominal aortic aneurysm; however, these results may be outdated, as smoking has declined and treatment has improved since the studies were completed. Results on screening for atrial fibrillation and other preclinical CVDs have not yet been published. In summary, the current evidence indicates that screening for CVD risk factors does not reduce the CVD burden.

Keywords

SYSTEMATIC REVIEW, MASS SCREENING, CARDIOVASCULAR DISEASES, MORTALITY, POPULATION, NATIONAL SCREENING PROGRAMME

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ABBREVIATIONS

AAA	abdominal aortic aneurism
AF	atrial fibrillation
CAC	coronary artery calcification
CIS	Commonwealth of Independent States
CP	carotid plaque
CVD	cardiovascular disease
ESC	European Society of Cardiology
IHD	ischaemic heart disease
NCD	noncommunicable disease
PAD	peripheral arterial disease
RCT	randomized controlled trial
SCORE	Systematic Coronary Risk Estimation (tool)

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SUMMARY

The issue

Cardiovascular diseases (CVDs) are the main cause of death in the WHO European Region, accounting for nearly 4 million deaths (43% of all deaths) in 2016. Population-level screening is a public health strategy to reduce the burden of disease in society by identifying and managing preclinical disease or the risk factors of disease. In the screening pathway, early identification in people who have not sought medical attention for CVD symptoms is followed by appropriate management of positive cases. Several studies that examined systematic screening programmes for reducing the CVD risk in general populations have questioned their effectiveness. Therefore, a comprehensive analysis of the current evidence on the CVD burden and the impact and potential adverse effects of screening for CVD risk factors and preclinical CVDs (including health economic considerations) is needed to inform national and regional decision-makers about feasible interventions for national screening programmes.

The synthesis question

The objective of this report is to address the question: “What is the effectiveness of systematic population-level screening programmes for reducing the burden of cardiovascular diseases?”

Types of evidence

A systematic review of peer-reviewed and selected grey literature in English and Russian was conducted between March and May 2020 to identify population-level randomized controlled trials (RCTs) examining the impact of screening for CVD risk factors (both behavioural factors (smoking, harmful use of alcohol, unhealthy nutrition and physical inactivity) and biological factors (high blood pressure, raised blood sugar, dyslipidaemia and raised body mass index)) preclinical CVD conditions (abdominal aortic aneurysm (AAA), atrial fibrillation (AF), peripheral arterial disease (PAD), coronary artery calcification (CAC) and carotid plaques (CPs)) on reducing the CVD burden (mortality, morbidity and costs) in general populations. No geographical or time limits were applied and only RCTs that included randomization, interventions related to CVD risk factors and/or preclinical CVD conditions and impact analysis at a population level were considered.

Results

A total of 33 studies were identified; these related to 22 RCTs, of which 14 focused on screening for CVD risk and CVD risk factors (two ongoing), four on AAA, two on AF (both ongoing) and two on a combination of preclinical CVDs (one ongoing). Following an assessment of methodological quality, all studies were included in a narrative synthesis, and a subset of studies with appropriate outcome data was included in a series of meta-analyses. In addition, one case study from Sweden was selected to illustrate a possible model for a population-level screening programme for AAA.

Based on several high-quality RCTs that included a large number of participants, the overall results clearly showed that screening for CVD risk and CVD risk factors has had no impact on lowering CVD morbidity and mortality in the general population. Moreover, serious adverse effects were identified (e.g. increased mortality). These studies were primarily conducted in western European countries, and the evidence can be difficult to transfer to other settings, such as south-eastern Europe and the Commonwealth of Independent States (CIS), owing to differences in national health-care systems and disease burdens. However, no high-quality RCTs have been conducted in these parts of the WHO European Region. There is, therefore, no evidential basis to recommend population-level screening for CVD risk and CVD risk factors in Member States of the Region.

At present, the benefit of screening for AAA is uncertain. Although some studies have reported reductions in AAA-related negative outcomes, there was no reduction in total mortality. However, recent changes in risk factors and less traumatic treatment may negate the apparent effects of AAA screening. Similarly, the results of ongoing population-level RCTs are needed to establish whether screening for AF can lower the CVD burden. Although one study on screening for a combination of preclinical CVDs showed promising results for reducing mortality, more evidence is needed to determine the effect of such programmes.

Policy considerations

Based on the review findings, the main policy considerations for Member States of the WHO European Region are to:

- review existing systematic population-level screening programmes for CVD risk and CVD risk factors (if such already exist), avoid initiating new screening programmes for CVD risk and CVD risk factors, and consider

alternative methods to achieve the desired outcomes in reducing the CVD burden;

- re-evaluate current systematic population-level programmes for screening for AAA, taking into account the changes in risk factors and improved treatment; and
- await the results of population-level RCTs on the effectiveness of screening for AF and other preclinical CVDs before considering the implementation of such programmes.



1. INTRODUCTION

1.1 Background

1.1.1 CVDs in the WHO European Region

CVDs are a diverse range of diseases that include cerebrovascular disease, heart failure, heart rhythm disturbances (such as AF), ischaemic heart disease (IHD), PAD and valvular heart disease. CVDs are currently the main cause of death in the WHO European Region: in 2016 they accounted for nearly 4 million deaths (43% of all deaths) (1). Within the Region, CVD mortality increased from 1990 to 1994 and then decreased, with a faster rate of decline from 2003 onwards. The CVD mortality rate has steadily decreased in Member States of the European Union since the 1980s and in south-eastern European countries since the 1990s. In the CIS, the CVD mortality rate increased throughout the 1990s but has been declining since 2003 (2,3). Modelling studies in several European countries have explored the possible causes of the decline in CVD mortality. These have shown that improved treatment explains one third to half of the reduction and an overall decrease in risk factors explains from half to two thirds (3), despite increases in the prevalence of obesity and type 2 diabetes. In the Region, the CVD morbidity rate – measured as hospital discharge with CVD – increased until 2004 and levelled off thereafter (3). By comparison, the CVD morbidity rate continued to increase in south-eastern Europe until 2007 and in the CIS until 2013. This levelling off in CVD morbidity is probably a result of improved health care and a decline in some risk factors, counteracted by increased longevity. However, considerable variations in CVD morbidity and mortality exist across Europe. Disability-adjusted life-years are an aggregate indicator of years lost due to premature death and years of healthy life lost due to disability: in 2017 CVDs accounted for 64 million disability-adjusted life-years (23% of the total) in Europe (4). Sex differences can be observed for CVD morbidity and mortality: men have a higher mortality risk, while women more often experience disability from CVD (3). In 2015 the total costs of CVDs in the Region were €210 billion, of which 53% were direct health costs (4).

Over seven decades of research, several modifiable and non-modifiable risk factors for CVD have been identified. Individual modifiable risk factors are smoking, unhealthy nutrition, physical inactivity, harmful use of alcohol, dyslipidaemia, raised body mass index, raised blood sugar and high blood pressure (hypertension); these can explain 75% of IHD (5,6). Non-modifiable risk factors are age, sex, ethnicity, hereditary factors and familial occurrence (including familial hypercholesterolaemia (7)). Preclinical CVDs include AAA, AF, CAC, CPs and PAD.

Population-level screening is a public health strategy to reduce the burden of diseases in society by identifying preclinical disease or risk factors for disease early among persons who have not sought medical attention for disease symptoms (8) or are not aware of any symptoms. Preventive interventions or treatment can then be applied to reduce mortality and morbidity rates. In a systematic programme of population-level screening and/or health checks, a predefined, apparently healthy population is approached in an organized and quality-assured way. The process starts by identifying people who are eligible for screening and then invites them for screening, refers positive cases for diagnosis, intervention, treatment and follow-up, and ends by reporting the outcomes (9). This should not be confused with case-finding, which is conducted in daily clinical practice and involves assessing patients indicated to be at risk of a condition when they seek help from the health-care system. Case-finding is an integrated part of the health-care system in any country, whereas systematic screening is a specific systematic programme in which the authorities invite citizens to participate (9). This report focuses on the latter.

Popular beliefs about systematic screening are that early detection equals better prognosis and that, theoretically, screening can lead to a reduction in the burden of diseases; however, there are also risks because not all screening programmes are beneficial. The task of any public health service is to identify beneficial programmes by appraising the evidence (10). Adverse effects of screening are reported as overdiagnosis, misdiagnosis and causing a false sense of security (11). Therefore, it is important to only initiate systematic screening when specific criteria are met. In 1968 WHO published the first overview of guidelines on the principles and practice of systematic screening for diseases (12). Since then, several more criteria have been suggested; an updated overview of criteria for systematic screening programmes was published in 2008 (Box 1) (13). To be effective on a population level, a systematic screening programme should reduce morbidity and/or mortality of the disease in question without causing unacceptable adverse effects (9). The programme should also be acceptable to citizens and conducted at a reasonable cost.

Box 1. Overview of proposed screening criteria, 1968–2008

1. The screening programme should respond to a recognized need.
2. The objectives of screening should be defined at the outset.
3. There should be a defined target population.
4. There should be scientific evidence of screening programme effectiveness.
5. The programme should integrate education, testing, clinical services and programme management.



Box 1 contd

6. There should be quality assurance, with mechanisms to minimize the potential risks of screening.
7. The programme should ensure informed choice, confidentiality and respect for autonomy.
8. The programme should promote equity and access to screening for the entire target population.
9. Programme evaluation should be planned from the outset.
10. The overall benefits of screening should outweigh the harm.

Source: Andermann et al., 2008 (13).

1.1.2 Strategies to promote cardiovascular health

WHO Member States have endorsed global and regional strategies and action plans for the prevention and control of noncommunicable diseases (NCDs) (14,15). Their implementation is monitored through the global monitoring framework, which includes a set of nine voluntary NCD targets, including those related to reductions in NCD premature mortality and in the prevalence of diabetes, hypertension and obesity (16). Furthermore, Sustainable Development Goal 3 includes target 3.4.1 to reduce premature mortality (between 30 and 70 years of age) from four major NCDs (cancer, chronic respiratory disease, CVD and diabetes) by a third in 2030 (17).

As part of the Global Action Plan for the Prevention and Control of Noncommunicable Diseases 2013–2020 (14), WHO identified a set of cost-effective (NCD “best buys”) and other recommended interventions for the prevention and control of NCDs. These can be implemented in Member States, as appropriate to their national contexts (18). These include an NCD best buy on CVD risk and CVD risk factor assessment and management that recommends drug therapy and counselling for individuals with a history of stroke or heart attack or individuals at high risk of a cardiovascular event within the next 10 years. The Noncommunicable Disease Integrated Prevention and Control programme of the WHO Regional Office for Europe is leading a cross-programmatic initiative to increase the effectiveness, maximize the benefits and minimize the harm of screening. A short guide on screening and a policy brief (9,19) were launched at the 2020 WHO European Conference on Screening (20).

1.1.3 Objectives of this report

Several studies that examined systematic population-level screening programmes for reducing the CVD risk in populations (e.g. the Inter99¹ trial (21)) have questioned their effectiveness in reducing the CVD burden in society. They are supported by a 2019 Cochrane review on the effectiveness of systematic offers of health checks (i.e. multiple tests in a non-symptomatic individual) that included studies both on a population level and targeting specific groups (22). The review concluded that these are not likely to reduce the burden of morbidity and mortality and may lead to overtreatment. This report builds on the Cochrane review by including evidence from more recent studies and on studies focusing more specifically on the effect on the CVD burden at population level (including health economic considerations) and assessing potential adverse effects of systematic population-level screening for CVDs. Thus, this systematic review assesses the impact of systematic population-level screening programmes on the CVD burden (mortality, morbidity and costs). It focuses on CVD risk and CVD risk factors, including screening for single and multiple risk factors (e.g. using a risk score) and for preclinical CVD conditions (i.e. AAA, AF, CAC, CPs and PAD). It aims to inform both national and regional decision-makers who are involved in, or considering implementation of, systematic screening to reduce CVDs in the WHO European Region.

1.2 Methodology

A systematic review of peer-reviewed and selected grey literature was conducted between March and May 2020 in English and Russian. No language or time restrictions were applied in the study selection. The methodological quality of included studies was appraised and outcomes were analysed narratively or through a meta-analysis of comparable outcomes.

The search of peer-reviewed literature retrieved 6191 records in English after removal of duplicates and five records in Russian. The search of grey literature retrieved 682 records. Of these, 93 articles were selected for full-text review, with 10 further studies identified during this process. In all, 33 studies (representing 22 RCTs) fulfilled the criteria for inclusion (21,23–54). Annex 1 provides further details of the search and selection strategy. Annexes 2–5 give the full details of studies examined, selected and excluded.

1. Full title: A Randomised Non-pharmacological Intervention Study for Prevention of Ischaemic Heart Disease Inter99



2. RESULTS

Section 2.1 presents the study characteristics of all included studies. Sections 2.2 and 2.3 present the results from both the narrative analysis and meta-analyses: for outcomes where meta-analysis was possible, the results of the meta-analyses are presented; for outcomes where meta-analysis was not possible, the results are presented narratively.

2.1 Study characteristics

2.1.1 Screening for CVD risk and CVD risk factors

Of the 22 included RCTs, 14 concerned the effectiveness of screening for CVD risk and CVD risk factors (reported in 23 studies (21,23–44)). See Annex 4 for a full list of studies with references. No RCTs were identified through the searches in Russian. Follow-up data were available for 12 RCTs: four in Sweden reported in five studies (31,32,38,39,42), four conducted in the United Kingdom (reported in five studies (27,28,30,40,41)), three in Denmark (reported in 10 studies (21,23,24,25,26,33,34,35,36,37)) and one in the former East Germany (29). Two RCTs are ongoing: one in Denmark (43) and the other in India (44). Age groups ranged from 18 to 65 years, but most RCTs focused on narrower age groups (e.g. 40–59 years). Three RCTs reported follow-up over 20 years; across all RCTs, follow-up ranged from one to 30 years. A total of 174 073 participants were included, with five RCTs including only men ($n = 36\,396$). Baseline data were collected between 1963 and 2001; eight RCTs collected data before 1990. Although the interventions varied, all RCTs comprised a health check (including clinical examinations, laboratory tests and questionnaires), followed by health counselling and initiation of medical treatment when hypertension or hypercholesterolaemia was identified. Two of the RCTs with follow-up used a risk score (21,30), and the remainder assessed several relevant risk factors. No studies focused solely on hypertension and none focused on screening for familial hypercholesterolaemia. For most studies, the risk of bias was judged as “low” or only as raising “some concerns”. See Annex 3 for an assessment of the bias risk and Annex 4 for a description of the data extracted from each study.

Two of the 14 RCTs are ongoing (43,44). The Check your Health RCT is designed to investigate the impact of offering preventive health checks (including screening for behavioural and clinical measures) and calculating a risk score to adults aged 30–49 years in Denmark (43). The second RCT is evaluating a community-based intervention on prevention of stroke mortality among individuals aged 50 years

or older in 32 rural villages in India (44). In the latter, participants will be screened for diabetes, hypertension and stroke, and followed up with treatment and home visits. See Annex 4 for a detailed description of both RCTs.

2.1.2 Screening for preclinical CVDs

Of the 22 included RCTs, eight focused on preclinical CVDs (reported in 10 studies (45–54)). See Annex 4 for a full list of studies with references. Of these, four focused on AAA (reported in six studies (45–50)), two on AF (both of these are ongoing) (51,52) and two on combined screening for preclinical CVDs (one is ongoing) (53,54).

Screening for AAA. Of the four RCTs on the effectiveness of screening for AAA, two took place in the United Kingdom (the Chichester study (45–47) and the Multicentre Aneurysm Screening Study (48)), one in Australia (50) and one in Denmark (49). All RCTs were initiated in the late 1980s and 1990s, and the interventions consisted of abdominal ultrasonographic screening. Follow-up ranged from five to 15 years. The total number of participants in all four RCTs was 134 271; of these, 9342 were women. The age groups investigated ranged from 64 to 83 years. Most studies had a low risk of bias (see Annex 3). Annex 4 provides additional study details and describes the data extracted from each study.

Screening for AF. Both RCTs on the effectiveness of screening for AF are ongoing (51,52). The Swedish STROKESTOP trial,² initiated in 2012, involves population-level screening in two Swedish regions comprising more than 25 000 individuals aged 75–76 years (51). In the United States of America, the VITAL-AF trial³ will test whether screening for AF results in increased detection of AF after one year and in a reduced stroke incidence after two years (52). Participants are aged 65 years or older. The intention is to include more than 16 000 patients in each study arm. Enrolment was initiated in July 2018.

Screening for other preclinical CVDs. Two RCTs were identified on combined screening for preclinical CVDs (53,54), both in Denmark; of these, one is ongoing (54). The RCT with follow-up investigated screening for AAA, hypertension and PAD among 50 156 men aged 65–74 years (53). The ongoing DanCavas trial⁴ is a study of population-level screening for subclinical CVDs (AAA, AF, CAC and PAD) (54). It was initiated in 2014 and will follow 45 000 men aged 65–74 years over 10 years.

2. Full title: Systematic ECG Screening for Atrial Fibrillation Among 75 Year Old Subjects in the Region of Stockholm and Halland, Sweden.

3. Full title: Screening for Atrial Fibrillation in an Ambulatory Clinic Population: the VITAL-AF Study.

4. Full title: Danish Cardiovascular Screening Trial II.



2.2 Population-level screening for CVD risk and CVD risk factors

In the identified studies as a whole, the main outcomes of population-level screening for CVD risk and CVD risk factors were morbidity and mortality, health-care utilization, disability pension and certified sickness absence, and adverse effects.

2.2.1 Morbidity and mortality

Findings from the reviewed studies and the meta-analyses show that population-level screening for CVD risk and CVD risk factors does not reduce total mortality or morbidity and mortality from CVDs, IHD and stroke (21,23,24,29,31,32,38,41,42). Table 1 summarizes the findings of the meta-analyses and Annex 5 provides more detailed results.

Table 1. Summary of meta-analysis findings

Screen/outcome	Number of studies	Relative risk of disease	95% confidence interval
Screening for CVD risk/ risk factors			
Total mortality	9	1.00	0.97–1.03
CVD morbidity and mortality	2	1.02	0.95–1.10
CVD mortality	5	1.04	0.73–1.49
IHD morbidity and mortality	4	1.00	0.97–1.05
IHD mortality	2	1.00	0.90–1.12
Stroke morbidity and mortality	3	1.05	0.95–1.17
Screening for AAA			
Total mortality	4	0.99	0.98–1.00
AAA mortality	4	0.63	0.41–0.97
AAA rupture	2	0.66	0.40–1.09

2.2.2 Health-care utilization

Four studies reported changes in prescribed medications (27,30,35,40). However, there was no indication of increased or decreased use of medication related to CVDs (e.g. antihypertensive or lipid-lowering drugs). Three studies reported on whether screening for CVD risk and CVD risk factors could reduce the total number of hospitalizations (i.e. not only those related to CVDs) (38,40,41): of these, one reported fewer hospitalizations in the screened groups after 18 months (40), whereas the other two showed no reductions in hospitalizations (38,41). In two studies, screening for CVD risk and CVD risk factors did not seem to reduce the number of physician visits (40,41): one of these reported more physical examinations and laboratory investigations among participants in the screened groups compared with the unscreened group, but with no difference in the rates of presumptive diagnoses (40). Finally, one study reported that screening did not increase the number of contacts with the health-care system or reduce the average direct cost of health care per participant (25). Thus, population-level screening for CVD risk factors does not appear to reduce health-care utilization.


2.2.3 Disability pension and certified sickness absence

One study reported that screening did not reduce the proportion of participants receiving disability pension after five years (39). Two studies reported the effect on sickness absence (40,41): one reported a higher rate of long-term sickness absence (15 days or over) in the screened group compared with the unscreened group after 18 months, and the other showed no difference between the groups after nine years. Therefore, population-level screening for CVD risk and CVD risk factors does not appear to reduce the proportion of people who receive disability pension or are on certified sickness leave; however, in the short term, it may lead to a higher proportion of people on long-term sickness leave.

2.2.4 Adverse effects

One RCT found a higher incidence of deaths among women from diseases associated with behavioural risk factors in areas with high participation rates, indicating that screening may increase the risk of these outcomes (33,34). Another study reported a higher risk of stroke among the screened population compared with the unscreened group (23). These results suggest that a risk of adverse effects may arise from population-level screening for CVD risk.

Furthermore, no psychological adverse effects of screening for CVD risk and CVD risk factors have been identified (26,36). One study found no difference in the use



of selected psychotropic medications or in hospital admissions due to psychiatric diagnoses before and after screening (35). Thus, the available evidence suggests no psychological adverse effects related to introducing systematic population-level screening for CVD risk and CVD risk factors.

In addition, one study reported a lower uptake of screening for CVD risk and CVD risk factors among people with a lower socioeconomic status (37). As a consequence, possible preventive measures will be more readily available to people in higher socioeconomic positions. This has raised concerns about whether screening programmes can increase social inequalities.

2.3 Population-level screening for preclinical CVDs

Most of the evidence on the effectiveness of screening for preclinical CVDs was related to AAA, and most of the RCTs on AAA were complete. However, most RCTs on AF and other preclinical CVDs were ongoing, thus limiting the amount of available data on these conditions.

2.3.1 Screening for AAA

Three countries have published data on population-level screening for AAA: Australia, Denmark and England (United Kingdom) (45–50). Most of the studies on screening for AAA reported the effects on morbidity and mortality related to AAA and to the cost–effectiveness of interventions, as assessed by life-years gained.

Morbidity and mortality. The meta-analyses showed that population-level screening for AAA led to reductions in AAA mortality among men (45,48–50), but not to a reduction in AAA ruptures (45,48) or total mortality (45,48–50) among men. A study that included women did not find that screening reduced AAA mortality or AAA rupture in women (46,47).

Cost–effectiveness. A study from the United Kingdom reported that the mean incremental (i.e. additional) cost per person offered screening was £100 (range: £82–£118; approximately US\$ 133) at 10-year follow-up (48). A comparison of the additional cost with life-years gained (i.e. by the avoidance of AAA mortality) showed a mean incremental cost–effectiveness ratio for AAA mortality of £7600 (around US\$ 10 149; range: £5100–£13 000). However, no data were provided on the incremental cost–effectiveness for total mortality. A Danish RCT reported an incremental cost–effectiveness ratio for total mortality of €157 per life-year gained (around US\$ 186;

range: –€3292 to €4401) and an estimated €179 per quality-adjusted life-year gained (around US\$ 212; range: €–4083 to €4682) (50). The confidence limits indicated no evidence that screening was cost-effective for reducing total mortality.

In addition to these studies, Case study 1 describes a possible model for a population-level screening programme for AAA from Sweden.

Case study 1. The Swedish nationwide AAA screening programme

Aim of the programme

AAA are usually asymptomatic until they rupture, which is fatal in more than 80% of cases. Screening aims to detect AAAs before they rupture. Based on the results of four RCTs (45,48–50) showing that screening led to a reduction in AAA-related mortality, the Swedish AAA screening programme was introduced in 2006 and achieved nationwide coverage in 2015.

Content


When they reached 65 years of age, all men were invited for a single ultrasound scan of the abdominal aorta. AAA was defined as an aortic diameter of above 29 mm. Follow-up and treatment followed international criteria indicating that men with an AAA of diameter 30–54 mm should be followed up by lifelong ultrasound surveillance, and those with an AAA of diameter greater than 54 mm or growth rate of 10 mm per year should be referred for surgical treatment.

Coverage and results

Attendance during the first eight years was 84%. Screening was calculated to result in a reduction in AAA-related mortality, but with no reduction in total mortality (55). In 2014 AAA-related mortality was estimated to have been reduced by 39% since 2000 (six years before the screening programme was launched) (55). This corresponded to an annual reduction of 90 premature deaths from AAA.

Arguments for and against the programme

Arguments for the programme is that it fulfils most of the screening criteria (Box 1) and has a very high attendance rate. The programme appears to reduce AAA-related mortality (55,56), and one study claimed that the programme is cost-effective (55).



Case study 1 contd

Arguments against the programme are that results from the four RCTs, which took place in the 1980s and 1990s, may be outdated. The occurrence of AAA has since declined in most western European and North America countries, as well as in Australia and New Zealand, from 4–9% in the late 1990s and early 2000s to below 2% in the 2010s (56). This decline parallels the decline in smoking in Sweden, which is the major risk factor for AAA. In addition, less traumatic treatment methods for AAA have been introduced. There is a risk that screening may lead to overdiagnosis and overtreatment, as not all AAA continue to grow. Analyses focusing on the first three years of the Swedish national screening programme concluded that AAA screening in Sweden did not substantially contribute to the large observed reduction in AAA mortality and that the most of the reduction was caused by other factors such as reduced rates of smoking (57).

2.3.2 Screening for AF

No evidence was found to determine whether population-level screening for AF can reduce the incidence of stroke. Only two RCTs addressed this question and both are ongoing (51,52).

2.3.3 Screening for other preclinical CVDs

One study showed that combined screening for AAA, hypertension and PAD may slightly reduce total mortality, but not CVD mortality or AAA-related mortality (53). The results of another ongoing study are pending (54).


3. DISCUSSION

3.1 Strengths and limitations of this review

An important strength of this systematic review is its stringent approach to searching for, selecting, appraising, and analysing studies. Strict inclusion criteria were employed: studies had to be RCTs performed in a geographically well-defined population, randomized at population level before study initiation, and include an intention-to-treat evaluation method. These criteria ensured that only evidence on the outcomes of national screening programmes for CVD risk and CVD risk factors and preclinical CVDs at population level were included. The strength of the evidence was assessed by determining the risk of bias. A limitation of the review methodology is that authors of the studies were not contacted to provide missing information.

Compared with previous systematic reviews on CVD risk and CVD risk factors, this review included fewer studies (owing to the requirement for results to be analysed on a population level), but longer follow-up times (22,58). Despite these differences, there was good agreement with the findings of previous reviews. The review included studies initiated between the 1960s and the 2000s (i.e. both older and more recent studies) but, as most studies need at least 10 years of follow-up, more recent studies could not be included. However, older and newer studies had similar results. The evidence originated mainly from western European countries: only one study conducted in an eastern European country was identified (the former East Germany (29)). Therefore, the limited available evidence does not indicate that screening for CVD risk and CVD risk factors would be effective in eastern European settings. However, relevant evidence from eastern European countries is unlikely to be available soon because high-quality population-level RCTs take several years to reach a conclusion.

The only completed RCTs on screening for preclinical CVDs were related to AAA. The identified RCTs on AF and combined screening for preclinical CVDs are ongoing, so no data are available on their outcomes.



3.2 Contextual factors in the WHO European Region related to screening programmes for CVD risk and CVD risk factors

The review found that systematic population-level screening does not reduce total mortality or combined morbidity and mortality from CVDs, IHD and stroke and that screening for CVD risk and CVD risk factors does not reduce the number of new medications, the proportion of the population receiving a disability pension, or the number of physician visits or hospitalizations. These findings are in agreement with those of a Cochrane review of 15 large RCTs ($n = 251\ 891$) (22).

The review included evidence on systematic population-level screening for CVD risk and CVD risk factors, and not on case-finding in clinical practice. An alternative to population-level screening is the use of more targeted screening programmes, such as workplace interventions. However, studies conducted in factories have consistently shown that screening performed in a work setting does not reduce the CVD burden. An important study of this type was a large WHO trial on the multifactorial prevention of coronary heart disease that was initiated in 1971; took place in 40 pairs of factories in Belgium, Italy, Poland and the United Kingdom; and included 60 000 participants (59). After six years, no significant effects of the intervention on total IHD, IHD mortality, myocardial infarction morbidity and total deaths were observed. Therefore, these more targeted screening programmes do not appear to reduce the CVD burden.

The present report found that some risk of serious adverse effects (e.g. increased mortality) may arise from population-level screening for CVD risk, possibly as a result of overdiagnosis and overtreatment (22). It is usually recommended to follow clinical guidelines, such as European Society of Cardiology (ESC) guidelines, when planning a national screening programme; however, these guidelines were mainly developed for patient populations and not for general populations. In a Danish population-level study, the application of ESC clinical guidelines to the general population led to nearly half of the population aged between 40 and 60 years qualifying for medical preventive treatment (60); this finding suggests a considerable risk of overdiagnosis and overtreatment. A 2012 Cochrane review on screening and treatment for mild hypertension reports the possible negative effects of overtreatment (61). It concluded that this type of screening has not been shown to reduce mortality or morbidity, and that 9% of participants discontinued treatment because of its adverse effects. Another concern is that uptake of screening

programmes is smaller among people with a lower socioeconomic status (37), which may increase social inequality.


Although screening for CVD risk and CVD risk factors is not supported by the scientific literature, some countries have introduced such programmes (e.g. Albania, Austria, England (United Kingdom) and the Russian Federation). In some countries, the programmes have been criticized because of a lack of evidence to support systematic screening (62,63), not fulfilling their own goals (e.g. a participation rate of at least 75%) (64,65) and increasing social inequalities (66). In Norway, general screening of men and women aged 40–42 years was introduced in 1985 but abandoned in 1999 (67). It is difficult to get a current overview of the types of screening programmes that have been implemented in Europe and in which countries they exist because systematic information on such programmes is lacking.

In summary, the findings of this review correspond with previous research on the impact of systematic population-level screening for CVD risk and CVD risk factors on reducing the CVD burden in society. Consequently, introducing national or regional screening programmes for CVD risk and CVD risk factors seems to have no beneficial effect.

3.2.1 Comparison with current prevention guidelines

Most guidelines on CVD prevention relate to case-finding, that is, when a patient is already in contact with the health-care system. In this situation, it is relevant to measure factors such as the patient's pulse, blood pressure and cholesterol level. However, in systematic population-level screening, health authorities invite citizens to come for screening via a national or regional programme. Therefore, what may benefit a patient seeking help in the health-care system seems not to be beneficial in the context of a population-level screening programme.

Guidelines from various organizations on CVD prevention are widely used by health professionals in Europe. The recommendations on screening differ, and very few address systematic screening of the general population. ESC guidelines recommend screening programmes for hypertension to include all adults (68), and that systematic CVD risk assessment “may be considered” in men aged over 40 years and women aged over 50 years (69). The ESC does not recommend systematic screening of blood glucose levels in the general population to determine CVD risk (70). However, as shown in this review, the available evidence does not support the ESC recommendation on systematic population-level screening for hypertension. In accordance with the evidence identified in this review, the guidelines



of most organizations do not directly advocate systematic screening. For example, the United Kingdom National Screening Committee does not recommend screening for hypertension among children and young people (71) and does not recommend screening for hypertension and vascular risk among adults (72,73). The World Heart Federation advocates for screening for high-risk patients only (74), and the United Kingdom National Institute for Health and Clinical Excellence, the American Society of Hypertension and the International Society of Hypertension do not make direct recommendations for systematic population-level screening (75,76). Instead of recommending systematic screening, the general tendency is towards advocating for population-level initiatives such as taxation and a healthy environment to reduce the prevalence of CVDs (77).

WHO does not recommend population-level screening programmes for CVDs, but instead proposes targeting those in primary care who may be at a higher risk owing to age or the presence of a risk factor (i.e. case-finding). The WHO Package of Essential Noncommunicable Disease Interventions protocol for assessment and management of cardiovascular risk uses diabetes mellitus, hypertension and smoking as entry points to target people at higher risk in primary health care (77). The later HEARTS technical package on risk-based CVD management, which uses updated WHO risk prediction charts, takes a similar approach by using diabetes mellitus, hypertension and smoking as entry points for CVD risk assessment (78).

3.2.2 Social and physical determinants influence CVD risk factors

Social and physical determinants (e.g. available resources, infrastructure and social support) impact on the risk of developing CVDs, for example through behavioural risk factors such as high calorie intake, low physical activity, smoking and the harmful use of alcohol. Disease prevention strategies are based on the rationale that a small shift in CVD risk across an entire population could lead to a greater reduction in the disease burden than a large shift among those already at high risk (79). Population-level prevention strategies for NCDs include fiscal measures (i.e. taxation and subsidies); international, national and regional policy and legislation (e.g. smoke-free policies, rules for advertising, and food production); and local environmental changes that are “making the healthy choice the easy choice”, according to the 1986 WHO Ottawa Charter for Health Promotion (80). These strategies were further developed in the WHO Health in All Policies approach (81), which acknowledges that most aspects of health and well-being lie outside the health sector and are socially and economically formed. As literature on the impact of environmental changes on improving cardiovascular health is growing fast, recommendations to change the environment as the primary effort to reducing the

CVD burden represent a potentially powerful and cost-effective strategy (82–84) instead of population-level screening.


3.3 Contextual factors in the WHO European Region related to screening programmes for preclinical CVDs

3.3.1 Screening for AAA

The review found that screening for AAA reduces AAA mortality, but not AAA rupture or total mortality. These results are comparable to those of a 2007 Cochrane review (85), which included the same four RCTs (but with shorter follow-up periods). The Cochrane review concluded that screening of elderly men (aged over 65 years) reduced AAA-specific mortality by 40% after approximately three to five years of follow-up. The same was not found for women, but the studies may have had too few female participants to determine an effect. A previous meta-analysis of the same four studies reported a 2.7% reduction in total mortality after 15 years of follow-up (86), but this was not supported by the present review.

The identified studies reported the cost-effectiveness of screening for AAA on reducing AAA mortality, but not on reducing total mortality. A cost-effectiveness analysis of AAA screening in men (which failed to meet the inclusion criteria) estimated an absolute risk reduction of 9.6 men per 10 000 invited for each 1% in AAA prevalence (87). The report concluded that one-time screening was cost-effective for AAA in men aged 65 years in the context of current AAA epidemiology and management. However, it recommended that the budgetary impact should also be considered, as the costs of this type of screening must be taken from other activities.

The identified screening programmes for AAA fulfil most of the screening criteria (see Box 1) and have very high attendance rates. However, it is important to note that, besides age, the biggest risk factor for AAA is smoking (accounting for 75% of the AAA cases). However, the decline in smoking combined with less traumatic treatment (endovascular repair) means that the validity of the four RCTs that form the basis of current recommendations is questionable. These studies were initiated from 1988 to 1999; since then, the smoking prevalence in men has declined in many, but not all, European countries. Thus, the gain from screening for AAA is currently uncertain.



Based on data from the largest RCT on AAA (the Multicentre Aneurysm Screening Study), an estimated 176 men per 10 000 people invited (95% confidence interval: 150–202) are overdiagnosed (88). Out of 1334 people with screening-detected AAA, only 11.8% would be expected to avoid death, while the others would live longer as AAA patients (88). Moreover, as prevalence lowers, the benefit of screening decreases and overtreatment increases (57). Regarding the psychosocial consequences of AAA screening, having an AAA diagnosis may moderately impact physical health and perceived stress (89). Furthermore, a study that investigated the possibility of increased social inequality as a result of screening found social inequality in uptake, despite a high participation rate: 65.1% in the most deprived areas and 84.1% in the least deprived areas (90).

It is unclear why smoking and former smoking is not used as a first-step screening before ultrasound examination is offered, as is routine practice in the United States AAA screening programme (91). An article exploring the ethical issues of AAA screening concluded that population-level screening for AAA is ethically justified because there are more beneficial than harmful effects (92).

AAA screening programmes were recently initiated in Monaco, initiated in Sweden in 2006–2015 (55) and implemented in all countries of the United Kingdom in 2009–2013 (93,94). These programmes are all ongoing. The national programmes in Sweden and the United Kingdom are well described, including the age interval, year of initiation, quality assessment of the programmes, participation rate and effect. National programmes have also been debated but not introduced in Denmark, Finland, Italy and Norway (91).

Regarding current CVD prevention guidelines, both ESC guidelines and the United Kingdom National Screening Committee recommend systematic screening for AAA by ultrasound for men aged over 65 years (95,96). In contrast, WHO makes no recommendation on population-level screening programmes for AAA, and this is not mentioned in the WHO “best buys” (18).

3.3.2 Screening for AF

No evidence was identified on screening programmes for AF. Regarding current CVD prevention guidelines, both the ESC and the European Association of Cardio-Thoracic Surgery recommend that systematic screening for AF may be considered in persons aged over 75 years (97). In contrast, the United Kingdom National Screening Committee (98) does not recommend screening for three primary reasons: (i) different types of AF exist, and they may not have the same risk for

stroke; (ii) it is unclear whether treatment for AF is effective in people identified through screening; and (iii) it is not known whether screening for AF is superior to the current approach (99). Similarly, WHO does not make any recommendation regarding population-level screening programmes for AF, and this is not mentioned among the WHO “best buys” (18).

3.3.3 Screening for other preclinical CVDs

Only two included studies involved screening for other preclinical CVD conditions, and these included different combinations of preclinical CVD conditions (53,54). More studies are therefore needed to establish recommendation on screening for these conditions.

3.4 Future research

Studies into screening for CVD risk and CVD risk factors at population level in countries of the WHO European Region have consistently shown no beneficial effect, despite including several high-quality RCTs with large numbers of participants. This means that population-level screening fails to fulfil the most important screening criterion: that there should be scientific evidence of screening programme effectiveness (Box 1, item 4). However, the studies were primarily conducted in western European countries with well-functioning health-care systems, where case-finding and relevant management among high-risk patients is implemented in clinical practice and the population has general access to medicine and health insurance. The findings may not be transferable to other settings (e.g. eastern Europe and the CIS) owing to differences in national health-care systems, disease burdens and societal factors (which may affect the outcomes of screening programmes); it is possible that countries with weaker health-care systems may benefit from population screening. Therefore, to provide an evidential basis for relevant recommendations, high-quality population-level RCTs on screening for CVD risk and CVD risk factors need to be conducted in eastern European and CIS countries.

3.5 Policy considerations

Based on the review findings, the main policy considerations for Member States of the WHO European Region are to:

- review existing systematic population-level screening programmes for CVD risk and CVD risk factors (if such already exist), avoid initiating new screening



programmes for CVD risk and CVD risk factors, and consider alternative methods to achieve the desired outcomes in reducing the CVD burden;

- re-evaluate current systematic population-level programmes for screening for AAA, taking into account the changes in risk factors and improved treatment; and
- await the results of population-level RCTs on the effectiveness of screening for AF and other preclinical CVDs before considering the implementation of such programmes.

4. CONCLUSIONS

Population-level screening for diseases is a widely accepted health-care strategy, but a systematic review of the literature showed that screening for CVD risk and CVD risk factors does not lower CVD morbidity and mortality at population level. The proposed screening criteria state that before a population-level screening programme is introduced in a country, the effect should be documented. However, most countries have not initiated studies to determine whether population-level screening for CVD risk and CVD risk factors can lower the CVD burden. In countries where high-quality studies have been performed, the lack of effect is evident. Except for one study, these have been performed in western European countries. Given these findings, population-level screening programmes for CVD risk and CVD risk factors cannot be recommended in the WHO European Region, and countries that have introduced such screening programmes should reconsider their efforts. However, it is important to stress that these findings do not concern case-finding among patients who are in contact with the health-care system, according to national and international guidelines. Screening for AAA was found to reduce relevant outcomes for the burden of AAA, but the evidence may be outdated owing to changes in important risk factors (such as smoking) and improved treatment options. Thus, more context-specific evidence is needed before screening for AAA can be recommended. As RCTs of systematic population-level screening for AF and other preclinical CVD conditions are still in progress, it is not yet possible to base any conclusions on them. A more promising option may be to promote societal changes by health promotion, following the 1986 WHO Ottawa Charter and Health in All Policies approach, to ensure that healthy choices are the easy choices.

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ANNEX 1. SEARCH STRATEGY

NB: references are given in the main reference list.

Databases

Peer-reviewed documents in English and Russian were identified from CINAHL (Cumulative Index to Nursing and Allied Health Literature), Cochrane Central Register of Controlled Trials, Embase, McMaster's Health Evidence, MEDLINE and Scopus. Further searches for peer-reviewed documents in Russian were performed in the following databases: CyberLeninka, East View, Russian Science Citation Index, Scholar.ru and the Scientific Archive of the Russian Federation. Further documents were obtained by searching clinical databases (the WHO International Clinical Trials Registry Platform and ClinicalTrials.gov) and grey literature databases (OpenGrey and the United Kingdom Screening Programme). All searches were conducted between March and May 2020 and no geographical or time limits were applied.

Hand searches were conducted to identify studies on the adverse effects and empirical (i.e. not modelling) studies on the cost-effectiveness of screening, with Web of Science used for citation tracking for eligible studies. Existing reviews on the topic were examined to identify recent primary studies and reference lists of included studies and systematic reviews were examined to identify further records for inclusion in the analysis.

Search terms

Search terms in English

Searches were built on two previous Cochrane reviews, from 2017 and 2019 (22,100). Search terms relevant to CVDs were collected from the first (and supplemented with other relevant CVD search terms) and those relevant to systematic screening programmes (supplemented with other relevant search terms), and used *The Cochrane highly sensitive search strategies for identifying randomized trials in MEDLINE* (101). The original search terms from both Cochrane reviews had been prepared for MEDLINE through Ovid; these were converted for use in MEDLINE through PubMed (Table A1.1).

Table A1.1. English search terms and combinations for the search in MEDLINE

No.	Query	Number of hits
1	((("cardiovascular"[TIAB] OR "cv"[TIAB] OR "cvd"[TIAB] OR "coronary"[TIAB] OR "chd"[TIAB] OR "heart disease"[TIAB]) AND "risk"[TIAB] AND (estimat*[TIAB] OR assessment*[TIAB] OR scor*[TIAB] OR equation*[TIAB] OR calculat*[TIAB])))	85 197
2	"Cardiovascular Diseases"[MeSH:noexp]	144 586
3	cardiovascular disease*[TIAB]	172 072
4	"coronary disease"[MeSH:noexp]	130 494
5	heart disease*[TIAB]	174 133
6	((coronary[TIAB] AND disease*[TIAB]))	192 069
7	coronary risk*[TIAB]	5 470
8	cardiovascular risk*[TIAB]	67 063
9	"hypertension"[MeSH:noexp]	231 439
10	("Hyperlipidemias"[MeSH] OR "Dyslipidemias"[MeSH] OR "Hyperglycemia"[MeSH])	112 014
11	cholesterol[TIAB]	240 421
12	"Arteriosclerosis"[MeSH]	173 967
13	((arteriosclerosis[TIAB] OR atherosclerosis[TIAB]))	129 001
14	OR/1–13	1 153 388
15	stroke	330 380
16	"peripheral vascular diseases"	13 390
17	(ischaemic heart disease OR Myocardial Ischemia OR Myocardial infarction)	540 819
18	atrial fibrillation	81 100
19	abdominal aortic aneurism	156

Table A1.1 contd

No.	Query	Number of hits
20	(coronary artery calcification OR "Vascular Calcification"[MeSH])	10 752
21	("carotid plaques" OR "Carotid Stenosis")	19 057
22	("Angioplasty, Balloon"[MeSH] OR "balloon dilation" OR "balloon angioplasty" OR "Stents"[MeSH])	114 682
23	("Cerebral Revascularization"[MeSH] OR "Transmyocardial Laser Revascularization"[MeSH] OR "Myocardial Revascularization"[MeSH] OR revascularization OR revascularization)	129 660
24	(apolipoprotein OR "Apolipoproteins"[MeSH])	61 921
25	("Thrombolytic Therapy"[MeSH] OR thrombolysis OR alteplase OR "Anticoagulants"[MeSH] OR anticoagulant* OR embolysis OR "Thrombectomy"[MeSH] OR thrombectomy OR "Percutaneous Coronary Intervention"[MeSH] OR PCI OR "Percutaneous Coronary Intervention" OR congenital heart disease OR "Cardiovascular Abnormalities"[MeSH] OR "Cardiomyopathies"[MeSH])	657 840
26	OR/15–25	1 516 085
27	14 OR 26	2 210 109
28	("physical examination"[MeSH:noexp] AND ((annual[TI] OR gp[TI] OR periodic[TI] OR yearly[TI] OR routine[TI]) OR ((primary[TIAB] AND (care[TIAB] OR health care[TIAB]))) OR primary health*[TIAB] OR general practitioner*[TIAB] OR general practice[TIAB] OR family doctor*[TIAB] OR family practice*[TIAB] OR family physician*[TIAB])))	2 911
29	((((health check*[TI] OR healthcheck*[TI] OR annual physical*[TI] OR annual medical[TI] OR medical check*[TI] OR primary care check*[TI] OR wellness check*[TI] OR well care[TI] OR wellcare[TI] OR well woman[TI] OR well visit*[TI])))	5 299

Table A1.1 contd

No.	Query	Number of hits
30	((((annual[TI] OR periodic[TI] OR regular[TI] OR routine[TI] OR yearly[TI]) AND (check*[TI] OR health* exam*[TI] OR health evaluation*[TI] OR medical exam*[TI] OR physical exam*[TI] OR wellness check*[TI] OR gp visit*[TI] OR physician visit*[TI] OR doctor visit*[TI] OR doctors* visit*[TI] OR doctor* visit*[TI] OR office visit*[TI])))	39
31	((((annual[TI] OR yearly) AND (medical*[TI] OR physical*[TI])))	2 048
32	((((annual[TI] OR yearly[TI]) AND visit*[TI]))	118
33	((preventive*[TI] AND (care check*[TI] OR checkup*[TI] OR check-up*[TI] OR visit*[TI] OR exam*[TI] OR family doctor*[TI] OR gp[TI] OR family physician*[TI] OR general practitioner*[TI])))	1 027
34	((((multifactor*[TIAB] OR multifactor*[TIAB]) AND prevent*[TIAB]))	6 766
35	((multiphasic[TIAB] AND (screening[TIAB] OR test*[TIAB] OR tests[TIAB] OR testing[TIAB] OR check*[TIAB]))	1 900
36	"general health screening"[TIAB]	133
37	"multiphasic screening"[MeSH:noexp]	1 088
38	((alcohol[TIAB] OR "Alcohol Drinking"[MeSH] OR diet[TIAB] OR "diet"[MeSH]) OR smoking[TIAB] OR "smoking"[MeSH] OR tobacco[TIAB] OR "Tobacco Use"[MeSH] OR exercise[TIAB] OR "exercise"[MeSH] OR life style[TIAB] OR "life style"[MeSH] OR (weight reduction[TIAB] OR "Weight Reduction Programs"[MeSH] OR obesity[TIAB] OR "Obesity"[MeSH] OR physical activity[TIAB] OR physical inactivity[TIAB] OR "Sedentary Behavior"[MeSH]) AND (screen*[TIAB] OR "Mass Screening"[MeSH] OR check[TIAB] OR check*[TIAB] OR "Physical Examination"[MeSH]) AND (prevention[TIAB] OR preventive[TIAB] OR preventive[TIAB] OR "Primary Prevention"[MeSH]))	31 534

Table A1.1 contd


No.	Query	Number of hits
39	OR/28–38	50 035
40	“mass screening”[MeSH:noexp]	101 313
41	((general[TIAB] OR organized[TIAB] OR organized[TIAB] OR prevent*[TIAB] OR systematic[TIAB] OR annual[TIAB] OR yearly[TIAB] OR periodic[TIAB] OR regular[TIAB] OR routine[TIAB]) AND (screen*[TIAB] OR check*[TIAB] OR checkup*[TIAB] OR check-up*[TIAB]))	216 890
42	((health check*[TIAB] OR health screen*[TIAB]))	10 515
43	OR/40–42	296 591
44	“primary health care”[MeSH]	155 147
45	“family practice”[MeSH:noexp]	65 009
46	“physicians, primary care”[MeSH:noexp]	3 305
47	“general practice”[MeSH:noexp]	13 047
48	“physicians, family”[MeSH:noexp]	16 276
49	“general practitioners”[MeSH:noexp]	7 615
50	“outpatient clinics, hospital”[MeSH]	16 960
51	“ambulatory care”[MeSH:noexp]	42 452
52	“ambulatory care facilities”[MeSH]	54 247
53	“community health services”[MeSH]	299 000
54	“community health centers”[MeSH]	12 201
55	((primary[TIAB] OR communit*[TIAB]) AND (care[TIAB] OR health*[TIAB]))	520 266
56	((family practi*[TIAB] OR family doctor*[TIAB] OR family physician*[TIAB] OR gp*[TIAB] OR gps*[TIAB] OR general practi*[TIAB]))	163 954

Table A1.1 contd

No.	Query	Number of hits
57	((outpatient*[TIAB] OR ambulatory[TIAB]) AND (care[TIAB] OR healthcare[TIAB] OR clinic*[TIAB] OR service*[TIAB] OR facilit*[TIAB])))	147 361
58	OR/44–57	1 150 868
59	43 AND 58	55 127
60	39 OR 59	100 436
61	“randomized controlled trial”[PT]	501 912
62	“controlled clinical trial”[PT]	590 612
63	randomized[TIAB]	509 706
64	placebo[TIAB]	210 946
65	“clinical trials as topic”[MeSH: noexp]	190 273
66	randomly[TIAB]	328 467
67	trial[TI]	213 392
68	OR/61–67	1 280 253
69	(animals[MeSH] NOT humans[MeSH])	4 675 327
70	68 NOT 69	1 178 080
71	27 AND 60 AND 70	2 622

Search terms in Russian

Сердечно-сосудистые заболевания, ишемическая болезнь сердца, сердечно-сосудистый риск, артериальная гипертензия, атеросклероз, инсульт, нарушение мозгового кровообращения, инфаркт миокарда, гипертония, холестерин, липиды, липидный спектр, фибрилляция предсердий, мерцательная аритмия, аневризма абдоминального отдела аорты, кальцификация коронарных артерий, бляшка сонной артерии, каротидная бляшка, субклинический атеросклероз, диспансеризация, ежегодные



профилактические осмотры, скрининг, курение, здоровый образ жизни, профилактическое консультирование, терапевт, семейный доктор, диета, снижение веса, измерение артериального давления, сравнительные исследования, рандомизированные исследования, сердечно-сосудистые исходы

Study selection

The titles and abstracts of all studies identified in the searches were independently assessed for relevance by two reviewers (CUE and TJ for searches in English; OR and AA for searches in the Russian) and then the full text of each selected publication was examined to identify documents for final inclusion. Disagreements were resolved through consensus.

Inclusion and exclusion criteria were selected to identify studies that could simulate the scenario of a country introducing population-level screening.

Inclusion criteria were:

- used a pragmatic RCT design;
- reported outcomes for CVD burden;
- evaluated interventions of systematic population-level screening for CVD risk and CVD risk factors (behavioural factors: smoking, harmful use of alcohol, unhealthy nutrition and physical inactivity; biological factors: high blood pressure, raised blood sugar levels, dyslipidaemia and raised body mass index) or preclinical CVD conditions, followed by counselling and/or medical and surgical treatment (with no limit on the number of risk factors screened for);
- included general populations of children and/or adults;
- had a geographically well-defined study area, from which a random population sample in relevant age groups was invited for screening (with the remaining population used as the control group); and
- was an intention-to-treat analysis (evaluation included the whole group, regardless of whether some individuals failed to attend the screening).

Exclusion criteria were:

- specifically targeted older people
- included populations with known specific risk factors or diseases.

Of 6878 titles and abstracts screened after removal of duplicates, 6785 records were excluded and full-text assessment was carried out for 93 records. An additional 14 studies were identified during this process, primarily from the studies included in two systematic reviews of the effectiveness of screening for CVD (58,100) and a systematic review on the effectiveness of screening for AAA (85). A final set of 33 studies (representing 22 RCTs) were included in the narrative synthesis and 13 RCTs were included in the meta-analysis (Fig. A1.1). Annex 2 provides a list of the studies that were excluded following full-text screening, along with the reasons for excluding them. A case study was selected to illustrate a possible model for a national screening programme for AAA.

Quality appraisal

The methodological quality of included studies was appraised using the RoB 2 Cochrane risk-of-bias tool for randomized trials (102), which considers the risk of bias in five domains: (i) the randomization process; (ii) deviation from the intended intervention; (iii) missing outcome data; (iv) measurement of outcomes; and (v) selection of the reported results.

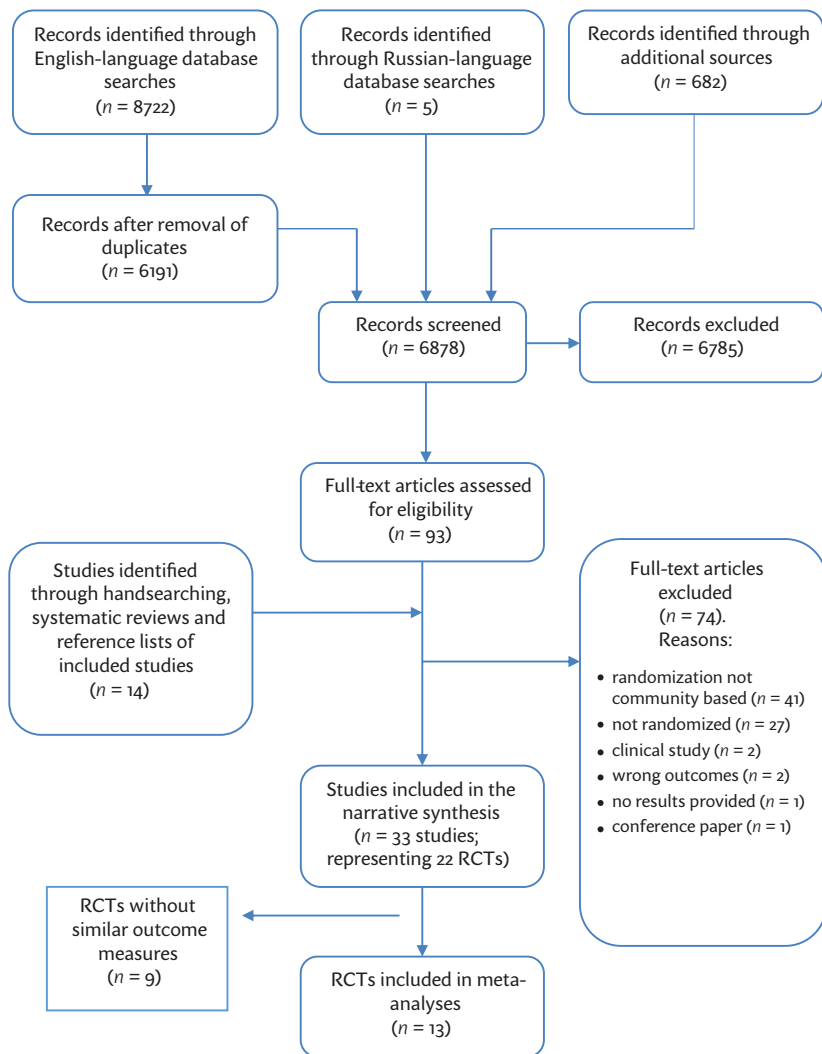
Data extraction

Based on a published framework (100), the following data were extracted from all included studies: design; geographical setting; country; start date and duration; diagnostic tests used; intervention; age and sex of participants, number of participants allocated to each arm, number of participants lost to follow-up for each outcome, baseline comparability. The following data were extracted from the study results: number of events or rates for mortality; and number of hospitalizations, surgical treatments, new medications and referrals to specialists; number of diagnostic procedures required because of positive screening tests; number of physician visits; and data on outcomes related to costs, morbidity and (long-term) adverse effects of interventions. Data were extracted independently by two authors, and disagreements were resolved by consensus.

Data analysis

Data were pooled from studies that reported similar outcome measures and used in a series of random-effects meta-analyses. Primary analyses included the number of cases in both the intervention and control groups; if absolute numbers were not reported, hazard ratios or relative risks were imputed. Sensitivity analyses were conducted to assess the effect of the risk of bias in the results. For outcomes where meta-analysis was not possible, data were analysed and presented narratively.

Fig. A1.1. Study selection process



ANNEX 2. STUDIES EXCLUDED AFTER FULL-TEXT REVIEW

Seventy-four studies were excluded after full-text review, for the reasons given. Where available, the formal name of each RCT is given; where not, the geographical location is given.

Table A2. Studies excluded after full-text review

Study ^a	Reference(s)	Reason
Screening for CVD risk and CVD risk factors		
ADDITION	<p>Charles MJ, Bruun NH, Simmons R, Dalsgaard E-M, Witte D, Jorgensen M et al. (2020). The effect of training GPs in motivational interviewing on incident cardiovascular disease and mortality in people with screen-detected diabetes. Results from the ADDITION-Denmark randomised trial. <i>BJGP Open</i>. 4(1):bigpopen20x101012. doi: 10.3399/bjgpopen20x101012.</p> <p>Echouffo-Tcheugui JB, Simmons RK, Prevost AT, Williams KM, Kinmonth AL, Wareham NL (2015). Long-term effect of population screening for diabetes on cardiovascular morbidity, self-rated health, and health behavior. <i>Ann Fam Med</i>. 13(2):149–57. doi: 10.1370/afm.1737.</p> <p>Griffin SJ, Borch-Johnsen K, Davies MJ, Khunti K, Rutten GEHM, Sandbæk A et al. (2011). Effect of early intensive multifactorial therapy on 5-year cardiovascular outcomes in individuals with type 2 diabetes detected by screening (ADDITION-Europe): a cluster-randomised trial. <i>Lancet</i>. 378(9786):156–67. doi: 10.1016/S0140-6736(11)60698-3.</p> <p>Griffin SJ, Rutten G, Khunti K, Witte DR, Lauritzen T, Sharp SJ et al. (2019). Long-term effects of intensive multifactorial therapy in individuals with screen-detected type 2 diabetes in primary care: 10-year follow-up of the ADDITION-Europe cluster-randomised trial. <i>Lancet Diabetes Endocrinol</i>. 7(12):925–37. doi: 10.1016/S2213-8587(19)30349-3.</p> <p>Simmons RK, Echouffo-Tcheugui JB, Sharp SJ, Sargeant LA, Williams KM, Prevost AT et al. (2012). Screening for type 2 diabetes and population mortality over 10 years (ADDITION-Cambridge): a cluster-randomised controlled trial. <i>Lancet</i>. 380(9855):741–8. doi: 10.1016/S0140-6736(12)61422-6.</p> <p>Simmons RK, Griffin SJ, Witte DR, Borch-Johnsen K, Lauritzen T, Sandbæk A (2017). Effect of population screening for type 2 diabetes and cardiovascular risk factors on mortality rate and cardiovascular events: a controlled trial among 1912,392 Danish adults. <i>Diabetologia</i>. 60(11):2183–91. doi: 10.1007/s00125-017-4323-2.</p>	Randomization not community based

Table A2 contd

Study ^a	Reference(s)	Reason
Screening for CVD risk and CVD risk factors		
Ashkelon Hypertension Detection and Control Program	Yosefy C, Dicker D, Viskoper JR, Tulchinsky TH, Ginsberg GM, Leibovitz E et al. (2003). The Ashkelon Hypertension Detection and Control Program (AHDC Program): a community approach to reducing cardiovascular mortality. <i>Prev Med.</i> 37(6 pt 1):571–6. doi: 10.1016/j.ypmed.2003.09.003.	Not randomized
Bucharest	Damsa T, Schioiu-Costache L, Georgescu M, Popescu A, Theodorini S, Teodorescu S et al. (1990). Evolution of ischemic heart disease risk factors in "The Bucharest Multifactorial Preventive Trial of Coronary Heart Disease" after 15-year follow-up. <i>Med Interne.</i> 28(3):229–33. PMID: 2092393. Steinbach M, Constantineanu M, Georgescu M, Harnagea P, Theodorini S, Galfi L et al. (1984). The Bucharest Multifactorial Prevention Trial of Coronary Heart Disease – ten year follow-up: 1971–1982. <i>Med Interne.</i> 22(2):99–106. PMID: 6740187. Steinbach M, Constantineanu M, Harnagea P, Theodorini S, Georgescu M, Mitu S et al. (1982). The Bucharest multifactorial prevention trial of coronary heart disease. General methodology and risk factor correction after five year follow-up (1971–1977). <i>Med Interne.</i> 20(2):117–36. PMID: 7123111. Steinbach M, Constantineanu M, Harnagea P, Theodorini S, Georgescu M, Mitu S et al. (1982). The Bucharest multifactorial prevention trial. The changes of morbidity and of general and specific mortality. <i>Med Interne.</i> 20(3):197–208. PMID: 7156815.	Not randomized
Behandla Blodtryck Bättre	Hansson L (1994). The BBB Study: the effect of intensified antihypertensive treatment on the level of blood pressure, side-effects, morbidity and mortality in "well-treated" hypertensive patients. <i>Behandla Blodtryck Bättre. Blood Press.</i> 3(4):248–54. doi: 10.3109/08037059409102265.	Clinical study

Table A2 contd

Study ^a	Reference(s)	Reason
Screening for CVD risk and CVD risk factors		
Diabetes Intervention Study	Hanefeld M, Fischer S, Schmechel H, Rothe G, Schulze J, Dude H et al. (1991). Diabetes Intervention Study. Multi-intervention trial in newly diagnosed NIDDM. <i>Diabetes Care</i> . 14(4):308-17. doi: 10.2337/diacare.14.4.308.	Randomization not community based
FINMONICA	Uusitupa M, Peltonen M, Lindstrom J, Aunola S, Ilanne-Parikka P, Keinänen-Kiukkaanniemi S et al. (2009). Ten-year mortality and cardiovascular morbidity in the Finnish Diabetes Prevention Study – Secondary analysis of the randomized trial. <i>PLOS ONE</i> . 4(5):e5656. doi: 10.1371/journal.pone.0005656.	Randomization not community based
Helsinki Businessmen Study	Miettinen TA, Huttunen JK, Naukkarinen V, Strandberg T, Mattila S, Kumlin T et al. (1985). Multifactorial primary prevention of cardiovascular diseases in middle-aged men. Risk factor changes, incidence, and mortality. <i>JAMA</i> . 254(15):2097-102. PMID: 4046137. Naukkarinen VA, Strandberg TE, Vanhanen HT, Salomaa VV, Sarna SJ, Miettinen TA et al. (1989). Mortality rates after multifactorial primary prevention of cardiovascular diseases. <i>Ann Med</i> . 21(6):441-6. doi: 10.3109/07853898909149236. Strandberg TE, Miettinen TA (1994). Multifactorial primary prevention: exploring the failures. <i>J Myocardial Ischemia</i> . 6:15-23. Strandberg TE, Raikonen K, Salomaa V, Strandberg A, Kautiainen H, Kivimäki M et al. (2018). Increased mortality despite successful multifactorial cardiovascular risk reduction in healthy men: 40-year follow-up of the Helsinki Businessmen Study intervention trial. <i>J Nutr Health Aging</i> . 22(8):885-91. doi: 10.1007/s12603-018-1099-0. Strandberg TE, Salomaa VV, Naukkarinen VA, Sarna SJ, Miettinen TA et al. (1995). Mortality in participants and non-participants of a multifactorial prevention study of cardiovascular diseases: a 28 year follow up of the Helsinki Businessmen Study. <i>Br Heart J</i> . 74(4):449-54. doi: 10.1136/hrt.74.4.449.	Randomization not community based

Table A2 contd

Study ^a	Reference(s)	Reason
Screening for CVD risk and CVD risk factors		
	Strandberg TE, Salomaa VV, Vanhanen HT, Sarna SJ, Miettinen TA et al. (1991). Long-term mortality after 5-year multifactorial primary prevention of cardiovascular diseases in middle-aged men. <i>JAMA</i> . 266(9):1225–9. PMID: 1870247.	Randomization not community based
J-DOIT3	Ueki K, Sasako T, Okazaki Y, Kato M, Okahata S, Katsuyama H et al. (2017). Effect of an intensified multifactorial intervention on cardiovascular outcomes and mortality in type 2 diabetes (J-DOIT3): an open-label, randomised controlled trial. <i>Lancet Diabetes Endocrinol</i> . 5(12):951–64. doi: 10.1016/S2213-8587(17)30327-3.	Randomization not community-based
Kaiser Permanente 1965	Friedman GD, Collen MF, Fireman BH (1986). Multiphasic Health checkup evaluation: a 16-year follow-up. <i>J Chronic Dis</i> . 39(6):453–63. doi: 10.1016/0021-9681(86)90112-8.	Randomization not community based
Mankato 1982	Murray DM, Luepker RV, Pirie PL, Grimm RH, Bloom E, Davis MA et al. (1986). Systematic risk factor screening and education: a community-wide approach to prevention of coronary heart disease. <i>Prev Med</i> . 15(6):661–72. doi: 10.1016/0091-7435(86)90071-x.	Wrong outcomes
MRFT	Multiple Risk Factor Intervention Trial for the Prevention of Coronary Heart Disease (MRFIT). ClinicalTrials.gov Identifier: NCT00000487 (https://clinicaltrials.gov/ctz/show/NCT00000487?term=NCT00000487&draw=2&rank=1 , accessed 21 October 2020).	Randomization not community based

Table A2 contd

Study ^a	Reference(s)	Reason
Screening for CVD risk and CVD risk factors		
	<p>Multiple Risk Factor Intervention Trial Research Group (1990). Mortality rates after 10.5 years for participants in the Multiple Risk Factor Intervention Trial. Findings related to a priori hypotheses of the trial. <i>JAMA</i>. 263(13):1795–801. doi: 10.1001/jama.1990.03440130083030.</p> <p>Eberly LE, Stamler J, Kuller LH, Neaton JD (2014). Multiple Risk Factor Intervention Trial. In: Balakrishnan N, editor. <i>Methods and applications of statistics in clinical trials: concepts, principles, trials, and design</i>, volume 1. Hoboken (NJ): John Wiley & Sons:577–86.</p> <p>Kuller L, Neaton J, Caggiula A, Falvo-Gerard L (1980). Primary prevention of heart attacks: the multiple risk factor intervention trial. <i>Am J Epidemiol</i>. 112(2): 185–99. doi: 10.1093/oxfordjournals.aje.a112984.</p> <p>Multiple Risk Factor Intervention Trial Research Group (1982). Multiple risk factor intervention trial. Risk factor changes and mortality results. <i>JAMA</i>. 248(12):1465–77. doi: 10.1001/jama.1982.03330120023025.</p> <p>Multiple Risk Factor Intervention Trial Research Group (1990). Mortality after 10 1/2 years for hypertensive participants in the Multiple Risk Factor Intervention Trial. <i>Circulation</i>. 82(5):1616–28. doi: 10.1161/01.cir.82.5.1616.</p> <p>Sherwin R, Kaelber CT, Kezdi P, Kjelsberg MO, Thomas HE Jr (1981). The multiple risk factor intervention trial (MRFIT) II. The development of the protocol. <i>Prev Med</i>. 10(4):402–25. doi: 10.1016/0091-7435(81)90058-x.</p> <p>Stamler J, Neaton JD, Cohen JD, Cutler J, Eberly L, Grandits G et al. (2012). Multiple risk factor intervention trial revisited: a new perspective based on nonfatal and fatal composite endpoints, coronary and cardiovascular, during the trial. <i>J Am Heart Assoc</i>. 1(5):e003640. doi: 10.1161/JAHA.112.003640.</p> <p>WHO European Collaborative Group (1983). Multifactorial trial in the prevention of coronary heart disease: 3. Incidence and mortality results. <i>Eur Heart J</i>. 4(3):141–7. PMID: 6345161.</p>	Randomization not community based

Table A2 contd

Study ^a	Reference(s)	Reason
Screening for CVD risk and CVD risk factors		
Multifactorial Prevention, Russian Federation	Тожиев МС, Норбеков МС, Шестов ДБ, и другие, Хван ЮЕ, Воробьев АМ, Теремов АА и другие (2004). Распространенность ишемической болезни сердца, основных факторов риска ее развития и эффективности многолетней многофакторной профилактики на предприятиях в ряде регионов России [Prevalence of ischemic heart disease, basic risk factors and efficacy of long-term multifactorial prophylaxis at work in some regions of the Russian Federation]. Терапевтический архив. 76(1):33–8 (in Russian). PMID: 15108435. Тожиев МС, Хван ЮЕ, Шестов ДБ, Таджиев ФС, Воробьев АМ, Очилова РХ и другие (2007). Распространенность артериальной гипертонии и эффективности многолетней многофакторной профилактики в ряде регионов России. [Prevalence of arterial hypertension and efficacy of long-term multifactorial prophylaxis in some regions of Russia]. Терапевтический архив. 79(1):27–32 (in Russian). PMID: 17385460. Тожиев МС, Шестов ДБ, Воробьев АМ, Теремов АА, Хоттиар ВП, Быков ИН и другие (2000). Распространенность ишемической болезни сердца, ее связь с основными факторами риска и эффективность многолетней многофакторной профилактики на промышленных предприятиях [Incidence of ischemic heart disease: its relation with the main risk factors and effectiveness of long-term multifactorial prevention at an industrial enterprise]. Терапевтический архив. 72(9):23–6 (in Russian). PMID: 11076411.	Not randomized

Table A2 contd

Study ^a	Reference(s)	Reason
Screening for CVD risk and CVD risk factors		
Multifactorial Prevention of Ischaemic Heart Disease, Russian Federation	Янушкевичус ЗИ, Глазунов ИС, Баубинене АВ, Граубаскас ВИ, Домаркиене СВ (1977). Методологическое исследование мультифакторной профилактики ишемической болезни сердца. [Methodological study of multifactorial prevention of ischemic heart disease]. Кардиология. 17(3):52–8 (in Russian). PMID: 886702. Kalinina, A (2014). Multifactor primary prevention of ischemic heart disease in middle-aged men and its efficacy (10-year follow-up). Rational Pharmacotherapy in Cardiology. 10(1):6–17. doi: 10.20996/1819-6446-2014-10-1-6-17. Kalinina A, Kontsevaaya AV (2014). Multifactor primary prevention of ischemic heart disease in middle-aged men and its efficacy (15-year follow-up). Rational Pharmacotherapy in Cardiology. 10(2): 134–46. doi: 10.20996/1819-6446-2014-10-2-134-146.	Not randomized
Multifactorial Prevention of Ischaemic Heart Disease in Men, Russian Federation	Мейманилиев ТС, Шлейфер ЕА, Мадаминов ЯК, Жильфанова ВШ, Айтмураева ГТ, Фингер ЕМ и другие (1990). Эффективность 5-летней программы по мультифакторной профилактике ишемической болезни сердца [Effectiveness of the 5-year program of multifactorial prevention of ischaemic heart disease in men]. Советская медицина. (12):57–9 (in Russian). PMID: 2151491.	Not randomized
New York 1971	Shapiro S, Fink R, Rosenberg C (1972). A program to measure the impact of multiphasic health testing on health differentials between poverty and non-poverty groups. Med Care. 10(3):207–14. doi: 10.1097/00005650-197205000-00003.	Randomization not community based

Table A2 contd

Study ^a	Reference(s)	Reason
Screening for CVD risk and CVD risk factors		
NHS Health Check	Caley M, Chohan P, Hooper J, Wright N (2014). The impact of NHS Health Checks on the prevalence of disease in general practices: a controlled study. <i>Br J Gen Pract.</i> 64(625):e516–21. doi: 10.3399/bjgp14X681013. Geue C, Lewsey JD, MacKay DF, Antony G, Fischbacher CM, Muir J et al. (2016). Scottish Keep Well health check programme: an interrupted time series analysis. <i>J Epidemiol Community Health.</i> 70(9):924–9. doi: 10.1136/jech-2015-206926.	Not randomized
Oslo study	Hjermann I, Velve Byre K, Holme I, Leren P (1981). Effect of diet and smoking intervention on the incidence of coronary heart disease. Report from the Oslo Study Group of a randomised trial in healthy men. <i>Lancet.</i> 2(8259):1303–10. doi: 10.1016/s0140-6736(81)91338-6. Holme I, Hjermann I, Helgeland A, Leren P (1985). The Oslo Study: diet and antismoking advice. Additional results from a 5-year primary preventive trial in middle-aged men. <i>Prev Med.</i> 14(3):279–92. doi: 10.1016/0091-7435(85)90057-x. Holme I, Retterstol IK, Norum KR, Hjermann I (2016). Lifelong benefits on myocardial infarction mortality: 40-year follow-up of the randomized Oslo diet and antismoking study. <i>J Intern Med.</i> 280(2):227–7. doi: 10.1111/joim.12485.	Randomization not community-based
OXCHECK 1989	Imperial Cancer Research Fund OXCHECK Study Group. (1991). Prevalence of risk factors for heart disease in OXCHECK trial: implications for screening in primary care. <i>BMJ.</i> 302(6784):1057–60. doi: 10.1136/bmj.302.6784.1057.	Randomization not community based
Prevention of Stroke in Urban China	Fang XH, Kronmal RA, Li SC, Longstreth WT Jr, Cheng XM, Wang WZ et al. (1999). Prevention of stroke in urban China: a community-based intervention trial. <i>Stroke.</i> 30(3):495–501. doi: 10.1161/01.str.30.3.495.	Not randomized

Table A2 contd

Study ^a	Reference(s)	Reason
Screening for CVD risk and CVD risk factors		
Salt Lake City 1972	Olsen DM, Kane RL, Proctor PH (1976). A controlled trial of multiphasic screening. <i>N Engl J Med.</i> 294(17):925–30. doi: 10.1056/NEJM197604222941705.	Not randomized
SHEP	SHEP Cooperative Research Group (1991). Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). <i>JAMA.</i> 265(24):3255–64. PMID: 2046107.	Clinical study
Titograd	Thorner RM, Djordjevic D, Vuckmanovic C, Pesic B, Culafic B, Mark F (1973). A study to evaluate the effectiveness of multiphasic screening in Yugoslavia. <i>Prev Med.</i> 2(2):295–301. doi: 10.1016/0091-7435(73)90072-8.	No results provided
Uppsala	Lithell H, Aberg H, Selinus I, Hedstrand H (1984). The primary preventive study in Uppsala. Fatal and non-fatal myocardial infarction during a 10-year follow-up of a middle-aged male population with treatment of high-risk individuals. <i>Acta Med Scand.</i> 215(5):403–9. PMID: 6741605	Not randomized
WHO Collaborative Trial of Multifactorial Prevention 1971	De Backer G, Kornitzer M, Dramaix M, Kittel F, Thilly C, M Graffar M et al. (1988). The Belgian Heart Disease Prevention Project: 10-year mortality follow-up. <i>Eur Heart J.</i> 9(3):238–42. doi: 10.1093/oxfordjournals.eurheartj.a062491. Kornitzer M, Rose G (1985). WHO European Collaborative Trial of multifactorial prevention of coronary heart disease. <i>Prev Med.</i> 14(3):272–8. doi: 10.1016/0091-7435(85)90056-8. Kornitzer M, De Backer G, Dramaix M, Kittel F, Thilly C, Graffar M et al. (1983). Belgian heart disease prevention project: incidence and mortality results. <i>Lancet.</i> 1(8333):1066–70. doi: 10.1016/s0140-6736(83)91908-6. Research Group of the Rome Project of Coronary Heart Disease Prevention. (1986). Eight-year follow-up results from the Rome Project of Coronary Heart Disease Prevention. <i>Prev Med.</i> 15(2):176–91. doi: 10.1016/0091-7435(86)90087-3. Rose G, Tunstall-Pedoe HD, Heller RF (1983). UK heart disease prevention project: incidence and mortality results. <i>Lancet.</i> 1(8333):1062–6. doi: 10.1016/s0140-6736(83)91907-4.	Randomization not community based

Table A2 contd

Study ^a	Reference(s)	Reason
Screening for CVD risk and CVD risk factors		
	Rywik S, Charzewska I, Szostak WB, Wagrowska H, Chabros E, Sobotowska M et al. (1980). [Polish experiment with regard to coronary disease prevention. I. Characteristics of the male population of the Warsaw industrial plants participating in the Coronary Disease Prevention Program]. <i>Kardiol Pol</i> . 23(1):41–9 (in Polish). PMID: 7366071.	Randomization not community based
	Sans Menendez S (1993). Ensayo randomizado de prevencion multifactorial de la cardiopatía isquemica [Randomized multifactorial prevention of ischaemic cardiopathy] [thesis]. Barcelona: Autonomous University of Barcelona (in Spanish).	
	World Health Organization European Collaborative Group (1974). An international controlled trial in the multifactorial prevention of coronary heart disease. <i>Int J Epidemiol</i> . 3(3):219–24. doi: 10.1093/ije/3.3.219.	
	World Health Organization European Collaborative Group (1986). European collaborative trial of multifactorial prevention of coronary heart disease: final report on the 6-year results. <i>Lancet</i> . 1(8486):869–72. PMID: 2870351.	
	World Health Organization European Collaborative Group (1990). WHO European Collaborative Trial in the multifactorial prevention of coronary heart disease. <i>IARC Sci Publ</i> . (103):123–31. PMID: 2279789.]	
Screening for AAA		
Sweden	Johansson M, Zahl PH, Siersma V, Jørgensen KJ, Marklund B, Brodersen J (2018). Benefits and harms of screening men for abdominal aortic aneurysm in Sweden: a registry-based cohort study. <i>Lancet</i> . 391(10138):2441–7. doi: 10.1016/S0140-6736(18)31031-6.	Not randomized; not RCTs
	Wanhainen A, Hultgren R, Linne A, Holst J, Gottsäter A, Langenskiöld M et al. (2016). Outcome of the Swedish Nationwide Abdominal Aortic Aneurysm Screening Program. <i>Circulation</i> . 134(16):1141–8. doi: 10.1161/CIRCULATIONAHA.116.022305.	

Table A2 contd

Study ^a	Reference(s)	Reason
Screening for CVD risk and CVD risk factors		
Screening for AF		
United Kingdom ^b	McCahon D, Fitzmaurice DA, Baker J, Murray ET, Iowett S, Sandhar H et al. (2014). Atrial fibrillation: is screening effective in identifying patients at risk of stroke? <i>Br J Haem.</i> 2014;165(Suppl 1):10–11.	Conference paper; probably not a RCT
Miscellaneous other studies		
Russian Federation	Калинина АМ, Ипатов ПВ, Кушунина ДВ, Егоров ВА, Дроздова ЛЮ, Бойцов СА (2016). Результаты выявления болезней системы кровообращения при диспансеризации взрослого населения: опыт первых 2 лет [Results of circulatory disease detection during prophylactic medical examination of the adult population: the first two years' experience]. <i>Терапевтический архив.</i> 88(1):46–52 (in Russian). doi: 10.17116/terarkh201688146-52. Калинина АМ, Кушунина ДВ, Горный БЭ, Антонов КА, Бегяева ОВ, Соколов ГЕ (2019). Потенциал профилактики сердечно-сосудистых заболеваний по результатам диспансеризации взрослого населения. [The potential of cardiovascular diseases' prevention according to the results of dispensary examinations of the adult population]. <i>Кардиоваскулярная терапия и профилактика.</i> 18(4):69–76 (in Russian). doi: 10.15829/1728-8800-2019-4-69-76. Яковлева ТВ, Вылегжанин СВ, Бойцов СА, Калинина АМ, Ипатов ПВ (2014). Диспансеризация взрослого населения Российской Федерации: первый год реализации, опыт, результаты, перспективы [Regular medical examination of adults in the Russian Federation: first year implementation: lessons learnt, results and perspectives]. <i>Социальные аспекты здоровья населения.</i> 4(38): 2 (in Russian).	Not randomized

Table A2 contd

Study ^a	Reference(s)	Reason
Screening for CVD risk and CVD risk factors		
Canada	Khan NA, McAlister FA, Campbell NR, Feldman RD, Rabkin S, Mahon J et al. (2004). The 2004 Canadian recommendations for the management of hypertension: Part II – Therapy. <i>Can J Cardiol.</i> 20(1):41–54. PMID: 14968142.	Not RCTs: commentary or reviews
Unonuma, Japan	Community health survey in Unonuma-region; Unonuma cohort study. Influence of diet and physical activity on progression of the metabolic domino: community-based and health checkup system-based prospective cohort-study (https://upload.umin.ac.jp/cgi-open-bin/icdr_e/ctr_view.cgi?recptno=R000016351 , accessed 21 October 2020).	Not RCTs: commentary or reviews
Singapore	Hughes K (1997). Screening for and treatment of hypercholesterolaemia: a review. <i>Ann Acad Med Singap.</i> 26(2):215–20. PMID: 9208077.	
Sweden	Samuelsson O (1985). Hypertension in middle-aged men. Management, morbidity and prognostic factors during long-term hypertensive care. <i>Acta Med Scand Suppl.</i> 702:1–79. PMID: 3866485.	
United States ^c	Upchurch G Jr (2007). [Commentary on] A sustained mortality benefit from screening for abdominal aortic aneurysm. <i>ACC Cardiosource Rev J.</i> 16:6–7.	
China, autonomous region of Tibet, and India	Ajay VS, Tian M, Chen H, Wu Y, Li X, Dunzhu D et al. (2014). A cluster-randomized controlled trial to evaluate the effects of a simplified cardiovascular management program in Tibet, China and Haryana, India: study design and rationale. <i>BMC Public Health.</i> 14:924. doi: 10.1186/1471-2458-14-924.	Randomization not community based

Table A2 contd

Study ^a	Reference(s)	Reason
Screening for CVD risk and CVD risk factors		
SCALE UP, Nairobi, Kenya	Oti SO, van de Vijver SJ, Kyobutungi C, Gomez GB, Charles Agyemang C, Moll van Charante EP et al. (2013). A community-based intervention for primary prevention of cardiovascular diseases in the slums of Nairobi: the SCALE UP study protocol for a prospective quasi-experimental community-based trial. <i>Trials</i> . 14:409. doi: 10.1186/1745-6215-14-409.	Wrong outcomes

ADDITION: Anglo-Danish-Dutch Study of Intensive Treatment in People With screenN Detected Diabetes in Primary Care; J-DOIT³: Japan Diabetes Optimal Integrated Treatment Study for 3 Major Risk Factors of Cardiovascular Diseases; MRFIT: Multiple Risk Factor Intervention Trial for the Prevention of Coronary Heart Disease; OXCHECK: Oxford and Collaborators Health CHECK Trial; SCALE UP: Sustainable model for Cardiovascular health by Adjusting Lifestyle and treatment with Economic perspective in settings of Urban Poverty, SHEP: Systolic Hypertension in the Elderly Program.

^a For Screening for CVD risk and CVD risk factors, the RCT name or geographical location is given; for the AAA/AF/ miscellaneous other studies, (mainly reviews and commentaries), the geographical location relates to the author affiliation.

^b Author affiliation: University of Oxford.

^c Author affiliation: University of Florida Health.

ANNEX 3. RISK OF BIAS IN THE INCLUDED STUDIES

The risk of bias was assessed, where possible, in the included studies using the RoB 2 Cochrane risk-of-bias tool for randomized trials (102). Tables A3.1–A3.3 describe the bias risk in 12 RCTs on screening for CVD risk factors, four RCTs on screening for AAA and one RCT on screening for other preclinical CVDs. Where available, the formal name of each RCT is given; where not, the geographical location is given. NB: references are given in the main reference list.

Table A3.1. Assessment of bias risk in the included studies on screening for CVD risk factors

Study, start year	Outcome(s) of interest	Bias risk: domain	Judgement of risk level	Reason for judgement
DanMONICA, 1982 (23)	Total mortality, IHD morbidity & mortality (combined), stroke morbidity & mortality (total)	Randomization process	Low	Randomization was done by computer Baseline characteristics were comparable
		Deviation from the intended interventions	Low	It was not possible to blind the intervention group, but the control group was never contacted The intervention aimed to change people's behaviour, and knowledge of being part of an intervention would probably not have led to bias Appropriate analyses were conducted
		Missing outcome data	Low	Outcome data were collected through registers containing complete follow-up data
		Measurement of the intervention	Low	Relevant ICD-10 codes were decided upon before conducting the analyses Register data were appropriate for outcomes on total mortality and on CVD morbidity & mortality
		Selection of the reported results	Low	Post hoc analysis, but an analysis plan (including selection of relevant ICD-10 codes) was made before the analyses were conducted
Overall			Low	–

Table A3.1 contd

Study, start year	Outcome(s) of interest	Bias risk: domain	Judgement of risk level	Reason for judgement
Ebeltoft, 1991 (24–26)	Total mortality, CVD morbidity & mortality (combined)	Randomization process	Low	Randomization was conducted independently of the investigators Baseline characteristics were comparable
		Deviation from the intended interventions	Some concerns	It was not possible to blind the intervention group GPs were not blinded, which could have had spill-over effects in the control group Appropriate analyses were conducted
		Missing outcome data	Low	Outcome data were collected through registers with complete follow-up
		Measurement of the intervention	Low	Relevant ICD-10 codes were decided upon before conducting the analyses Register data were appropriate for outcomes on total mortality, CVD morbidity & mortality
		Selection of the reported results	Low	Post hoc analysis, but relevant ICD-codes were selected before the analyses were conducted
		Overall	Some concerns	–

Table A3.1 contd

Study, start year	Outcome(s) of interest	Bias risk: domain	Judgement of risk level	Reason for judgement
Ely, 1990 (27,28)	Self-reported medication use (new medication)	Randomization process	Some concerns	The allocation sequence was random There were baseline differences between groups
		Risk of bias due to deviation from the intended interventions	High	Follow-up data were only available for 43% of participants It was not possible to blind the intervention group, and the control group was never contacted
		Missing outcome data	High	Follow-up data were only available for 43% of participants The analyses did not correct for potential bias arising from the missing outcome data
		Measurement of the intervention	High	Self-reported outcomes were not appropriate, considering the high attrition rate
		Selection of the reported results	Some concerns	Probably no pre-specified analysis plan for this outcome No rationale was provided for collecting self-reported data on medication use
Overall			High	–

Table A3.1 contd

Study, start year	Outcome(s) of interest	Bias risk: domain	Judgement of risk level	Reason for judgement
Erfurt-Süd, 1968 (29)	Total mortality, CVD mortality, IHD morbidity & mortality (combined), IHD mortality	Randomization process	Low	Participants were sorted alphabetically, but this was unlikely to result in bias
		Risk of bias due to deviation from the intended interventions	Low	It was not possible to blind the intervention group, but the control group was not informed about the trial
		Missing outcome data	Low	Follow-up through registries, hospital records and autopsies Only two participants left the study area
		Measurement of the intervention	Low	Appropriate method used to measure the outcome – unlikely to result in bias
		Selection of the reported results	Low	No indication of selective reporting
Family Heart ^a (30)	Prescription of medications (new medication)	Overall	Low	–
		Randomization process	Low	Randomization process not described in much detail, but participants were assigned to either intervention or control condition at the same time

Table A3.1 contd

Study, start year	Outcome(s) of interest	Bias risk: domain	Judgement of risk level	Reason for judgement
		Deviation from the intended interventions	Low	It was not possible to blind the intervention group, but the control group was not informed about the trial The intervention aimed to change people's behaviour, and knowledge of being part of an intervention would probably not lead to bias Control group unaware of the trial Cluster RCT design reduced the risk of contamination of the control group
		Missing outcome data	High	Significant loss to follow-up
		Measurement of the intervention	High	Lack of information on how measurement of prescriptions was made Assessment could have differed between groups
		Selection of the reported results	Some concerns	No information on analysis plan concerning this specific outcome
		Overall	High	–

Table A3.1 contd

Study, start year	Outcome(s) of interest	Bias risk: domain	Judgement of risk level	Reason for judgement
Gothenburg, 1963 (31)	Total mortality, CVD mortality	Randomization process	Low	Allocation was based on birth date but is not expected to compromise the randomization process Allocation took place before the intervention was given
		Deviation from the intended interventions	Low	It was not possible to blind the intervention group, but the control group was never contacted and the regular physicians of participants in the intervention group were not involved
		Missing outcome data	Low	The study report stated that “loss to follow-up by the end of 1977 was 0.3% in the experimental group and 1% in the control group”
		Measurement of the intervention	Mortality outcomes: low CVD mortality outcomes: high	Death certificates were assessed, and some were reclassified for cause of death Outcome assessors were not blinded to allocation status (22)

Table A3.1 contd

Study, start year	Outcome(s) of interest	Bias risk: domain	Judgement of risk level	Reason for judgement
Gothenburg, 1970 (32)	Total mortality, IHD morbidity & mortality (combined), stroke morbidity & mortality (combined), IHD mortality, stroke mortality	Selection of the reported results	Some concerns	Probably no pre-specified analysis plan
		Overall	Total mortality outcomes: some concerns	–
			CVD mortality outcomes: high	
		Randomization process	Low	Allocation was done by computer (22)
		Deviation from the intended interventions	Low	It was not possible to blind the intervention group Participants were randomized before contact Neither GPs nor the control group were contacted
		Missing outcome data	Low	Complete follow-up
		Measurement of the intervention	Low	Register data were used
		Selection of report results	Low	Pre-specified analysis plan
		Overall	Low	–

Table A3.1 contd

Study, start year	Outcome(s) of interest	Bias risk: domain	Judgement of risk level	Reason for judgement
Inter99, 1999 (21,33–37)	Total mortality, CVD morbidity & mortality (combined), stroke morbidity & mortality (combined), IHD morbidity & mortality (combined), new medications, hospitalization	Randomization process	Low	Randomization was by computer before any contact was made with participants
		Risk of bias due to deviation from the intended interventions	Low	It was not possible to blind the intervention group, but the control group was not informed about the trial. The intervention aimed to change people's behaviour, and knowledge of being part of an intervention group would probably not lead to bias. Appropriate analyses were conducted
		Missing outcome data	Low	Register data used
		Measurement of the intervention	Low	Pre-selected ICD-10 codes were used to measure the outcome
		Selection of the reported results	Low	Analyses were in accordance with a pre-specified analysis plan
Malmö, 1969 (38,39)	Total mortality, CVD mortality, hospitalization, disability pension	Overall	Low	–
		Randomization process	Low	Allocation was based on birth date but is not expected to compromise the randomization process. It also took place before delivery of the intervention
		Deviation from the intended interventions	Low	It was not possible to blind the intervention group, but the control group and their regular physicians were not informed about the trial

Table A3.1 contd

Study, start year	Outcome(s) of interest	Bias risk: domain	Judgement of risk level	Reason for judgement
Northumberland, 1969 (40)	Hospitalizations, number of physician visits, new medication, diagnostic procedures, certified sickness	Missing outcome data	Low	99% follow-up on mortality
		Measurement of the intervention	Low	The outcome assessor was not aware of allocation (22)
		Selection of the reported results	Low	No indication of selective reporting
		Overall	Low	–
		Randomization process	Some concerns	Allocation was based on birth date but is not expected to compromise the randomization process. Baseline data were based on GP records, and GPs were aware of the allocation status
		Deviation from the intended interventions	Some concerns	GPs treated both intervention and control participants leading to risk of contamination. Probable that participants were analysed as part of the group they were assigned to
		Missing outcome data	Low	90.2% of participants cooperated fully; 5.2% cooperated partially
		Measurement of the intervention	High	Outcome assessment could have been influenced by knowledge of allocation status
		Selection of the reported results	Some concerns	Lack of information on a pre-specified analysis plan
		Overall	High	–

Table A3.1 contd

Study, start year	Outcome(s) of interest	Bias risk: domain	Judgement of risk level	Reason for judgement
South-East London, 1967 (41)	Total mortality, CVD mortality, hospitalizations, physician visits, certified sickness	Randomization process	High	Unclear description of allocation process. Allocation took place before delivery of the intervention
		Deviation from the intended interventions	Some concerns	It was not possible to blind the intervention group, but this is not expected to result in bias due to the nature of the intervention. Due to emigration from the study site, the control group was invited for screening after 4 years, which was not planned
		Missing outcome data	Low	Data were available for most participants
		Measurement of the intervention	Total mortality & CVD mortality: low	Not likely to result in bias for outcomes measuring mortality and morbidity
			Physician visits & certified sickness: high	Originally, data were collected from health-care providers. Due to migration issues, this was supplemented with a survey
		Selection of the reported results	Low	No indication of selective reporting
		Overall	High	–

Table A3.1 contd

Study, start year	Outcome(s) of interest	Bias risk: domain	Judgement of risk level	Reason for judgement
Stockholm, 1969 (42)	Total mortality, CVD mortality	Randomization process	Low	Randomization was done by computer (22)
		Deviation from the intended interventions	Low	It is not possible to blind the intervention group, but this is not expected to result in bias due to the nature of the intervention. Appropriate analyses were conducted
		Missing outcome data	Low	All participants were followed up through registers
		Measurement of the intervention	Low	Follow-up through registers
		Selection of the reported results	Low	No indication of selective reporting
		Overall	Low	–

GP: general practitioner; ICD-10: 10th revision of the International Classification of Diseases; Inter99:

A Randomised Non-pharmacological Intervention Study for Prevention of Ischaemic Heart Disease Inter99.

^a No information given on when the baseline data were collected.

Table A3.2. Assessment of bias risk in the included studies on screening for AAA

Study, start year	Outcome(s) of interest	Bias risk: domain	Judgement of risk level	Reason for judgement
Chichester, 1989 (45–47)	AAA mortality, incidence of AAA rupture, total mortality	Randomization process	Low	Randomization was done by computer by an external research unit
		Deviation from the intended interventions	Low	It is not possible to blind the intervention group, but the control group was never contacted. Appropriate analyses were conducted
		Missing outcome data	Low	Outcome data were collected through registers
		Measurement of the intervention	Low	Register data are appropriate for outcomes on total mortality and incidence of AAA rupture & mortality
		Selection of the reported results	Low	Outcomes presented in the study correspond with those reported in the trial registration
		Overall	Low	–
Multicentre Aneurysm Screening Study, 1997 (48)	AAA-related mortality, AAA rupture, total mortality, costs	Randomization process	Low	Randomization was done centrally by computer
		Deviation from the intended interventions	Some concerns	Inconsistencies in the reported number of participants in the 4- and 10-year follow-up. Appropriate analyses were conducted
		Missing outcome data	Low	Close to complete follow-up. Data collected through registers

Table A3.2 contd

Study, start year	Outcome(s) of interest	Bias risk: domain	Judgement of risk level	Reason for judgement
Viborg, 1994 (49)	AAA mortality, total mortality, costs	Measurement of the intervention	Low	Register data are appropriate. Outcome assessors not aware of group allocation
		Selection of the reported results	Low	Reported outcomes correspond with the trial registration
		Overall	Some concerns	–
		Randomization process	Low	Allocation sequence was random
		Deviation from the intended interventions	Low	It is not possible to blind the intervention group, but the control group was never contacted. Appropriate analyses were conducted
		Missing outcome data	Low	Complete follow-up
		Measurement of the intervention	Low	Register data are appropriate. Outcome assessors were not aware of group allocation
		Selection of the reported results	Low	Reporting corresponds with the trial registration, and appropriate analyses were conducted
		Overall	Low	–

Table A3:2 contd

Study, start year	Outcome(s) of interest	Bias risk: domain	Judgement of risk level	Reason for judgement
Western Australia, 1996 (50)	AAA mortality, total mortality	Randomization process	Low	Randomization was done by computer
		Deviation from the intended interventions	Low	It is not possible to blind the intervention group, but the control group was never contacted. Appropriate analyses were conducted
		Missing outcome data	Low	Register data. Outcome assessor was not aware of group allocation
		Measurement of the intervention	Low	Register data is appropriate. Outcome assessor was not aware of group allocation
		Selection of the reported results	Low	No indication of selective reporting
Overall		Low	–	

Table A3.3. Assessment of bias risk in the included study on combined screening for preclinical CVDs

Study, start year	Outcome(s) of interest	Bias risk: domain	Judgement of risk level	Reason for judgement
Viborg Vascular, 2008 (53)	Total death, CVD-related death, AAA-related death	Randomization process	Low	Randomization was done by computer
		Deviation from the intended interventions	Low	It is not possible to blind the intervention group, but the control group was never contacted. Appropriate analyses were conducted
		Missing outcome data	Low	< 1% was lost to follow-up
		Measurement of the intervention	Low	Register data is appropriate. Outcome assessor and statistician were not aware of group allocation
		Selection of the reported results	Some concerns	Outcomes reported in the study do not correspond fully to what was registered with clinicaltrials.gov
Overall			Some concerns	–

ANNEX 4. DATA EXTRACTION

Tables A4.1–A4.4 describe the data extracted from the included studies on screening for CVD risk factors, AAA, AF and other preclinical CVD. Where available, the formal name of each RCT is given; where not, the geographical location is given. NB: references are given in the main reference list.

Table A4.1. Data extracted from included studies on screening for CVD risk

Study, start year: status	Data category	Description
DanMONICA, 1982 (23): completed	Study design	Parallel-group RCT
	Setting	11 municipalities in the western suburbs of Copenhagen
	Age and sex of participants	30–60 years at baseline; men and women
	Country	Denmark
	Date of study	Baseline data collected in 1982–1984
	Diagnostic tests used	Questionnaire (smoking, diet, physical activity, alcohol, family history), clinical examination (weight, height, blood pressure, pulse, ECG, lung function, ultrasound tests and other non-invasive tests), serum lipids and urine analysis
	Intervention	The intervention group was invited for three health checks over the 11-year study period; if needed, participants were referred to GPs
	Total study duration	30 years (mean: 25.2 years)
	Number of participants allocated to each arm	Intervention group, 4789; control group, 12 994
	Loss to follow-up	0%

Table A4.1 contd

Study, start year: status	Data category	Description
	Baseline comparability	Older men were intentionally oversampled in the intervention group – this was the only difference between groups at baseline. No difference when adjusted for age and sex
	Relevant outcomes	Total mortality, IHD morbidity & mortality (combined), stroke morbidity & mortality (combined)
	Results	Total mortality: HR = 1.03 (95% CI: 0.98–1.09) IHD morbidity & mortality: HR = 0.99 (95% CI: 0.92–1.07) Stroke morbidity & mortality: HR = 1.14 (95% CI: 1.04–1.25)
Ebeltoft, 1991 (24–26): completed	Study design	Parallel-group RCT
	Setting	9 GPs in Ebeltoft municipality
	Age and sex of participants	30–49 years on 1 January 1991; men and women
	Country	Denmark
	Date of study	Baseline data collected in 1991
	Diagnostic tests used	Questionnaire and assessment of blood tests for cholesterol, glucose and liver enzymes, blood pressure, BMI, carbon monoxide concentration in expired air, serum creatinine, ECG, family medical history, physical endurance, smoking, spirometry, and vision and hearing; a urinary dipstick for albumin and blood; and an optional HIV test

Table A4.1 contd

Study, start year: status	Data category	Description
	Intervention	<p>The 2000 invited people were divided a priori into three groups. Participants in:</p> <ul style="list-style-type: none"> • group A were offered a general health check at baseline and after 1 and 5 years, followed by mailed feedback in layman's terms; if necessary, a 10–15 minutes consultation was offered; • group B were offered the same and, irrespective of the general health check results, a 45-min baseline consultation with their GP to discuss health problems and encourage healthy lifestyle changes; and • group C received a questionnaire at baseline and a general health check at year 5. <p>All participants were offered an additional health check at the 15-year follow-up</p>
	Total study duration	24 years
	Number of participants allocated to each arm	<p>Invitees: 2000 (493 declined); intervention group A + B, 1006; control group, 501</p> <p>Non-invitees: 1464 (728 participants were censored after 15 years, as they were offered screening)</p>
	Loss to follow-up	0%
	Baseline comparability	No significant differences between invitees and non-invitees at baseline
	Relevant outcomes	Total mortality, CVD morbidity & mortality (combined)
	Results	<p>Comparing invitees to non-invitees:</p> <ul style="list-style-type: none"> • CVD morbidity & mortality: HR = 1.11 (95% CI: 0.88–1.41) • total mortality: HR = 0.93 (95% CI: 0.75–1.16)

Table A4.1 contd

Study, start year: status	Data category	Description
	Comments	<p>This synthesis review included the latest follow-up, which was a post hoc study after 24 years and the effect was analysed on a population basis. At the start of the study, the authors compared two intervention groups with a control group. As these analyses were not population-based, they were not included in the main analysis</p> <p>The screened and unscreened groups were also compared with an external control group consisting of 1 511 498 Danes living outside the municipality of Ebeltoft. This comparison was not included in this review because the analysis was not based on a randomization</p>
Ely, 1990 (27,28): completed	Study design	Parallel-group RCT
	Setting	1 GP in Ely
	Age and sex of participants	40–65 years; men and women
	Country	England, United Kingdom
	Date of study	Baseline data collected in 1990
	Diagnostic tests used	Blood pressure measurement, a 75-g oral glucose tolerance test, measurement of plasma lipids and HbA _{1c}
	Intervention	No standard intervention package was specified for people found to have type 2 diabetes or elevated CVD risk factors following screening. GPs were informed of the results and advised to take whatever action they thought necessary. Intervention group was screened 4 times
	Total study duration	13-year follow-up (mean: 12.5 years)
	Number of participants allocated to each arm	Screened group, 1705; unscreened group, 3231

Table A4.1 contd

Study, start year: status	Data category	Description
	Loss to follow-up for each outcome	Results based on re-examination after 10 years: 43% attendance rate
	Baseline comparability	No information
	Relevant outcomes	Self-reported medication use (new medication)
	Results	No difference in self-reported intake of antihypertensive drugs ($P = 0.98$), lipid-lowering drugs ($P = 0.2$), antiplatelet drugs ($P = 0.6$), or antidepressant ($P = 0.4$) and anxiolytic drugs ($P = 0.8$)
Erfurt-Süd, 1968 (29): completed	Study design	Parallel-group RCT
	Setting	District of Erfurt-Süd
	Age and sex of participants	50–54 years; men
	Country	Germany
	Date of study	Baseline data collected in 1968–1971
	Diagnostic tests used	Questionnaire, clinical examination, including standardized blood pressure measurement, ECG registration and chest X-ray, determination of various laboratory parameters (cholesterol and β -lipoprotein concentration and glucose after oral exposure)
	Intervention	3 repeated medical examinations, including the reporting of findings, clarification of the role of risk factors in CVD development and indications of behaviour change (smoking, high-calorie/high-fat diet, lack of exercise); high-risk individuals had a 5–6-week stay in a special department (to provide support for physical activity, diet, weight reduction, smoking cessation, psychotherapeutic treatment)
	Total study duration	9–10 years

Table A4.1 contd

Study, start year: status	Data category	Description
	Number of participants allocated to each arm	Intervention group, 314; control group, 600
	Loss to follow-up for each outcome	< 1%
	Baseline comparability	Not assessed: the control group was not contacted at baseline
	Relevant outcomes	Total mortality, CVD mortality, IHD morbidity & mortality (myocardial infarction), IHD mortality (myocardial infarction)
	Results (intervention group vs control group)	Total mortality: 11.2% vs 11.5% CVD mortality: 5.4% vs 4.2% IHD morbidity & mortality: 11.2% vs 8.2% IHD mortality: 3.8% vs 3.5% No differences were statistically significant
	Comments	Outcomes related to myocardial infarction were analysed together with IHD in other studies Two age groups were included in the study, but data were only extracted for the oldest age group owing to a breach of the randomization for the younger age group
Family Heart ^a (30): completed	Study design	Cluster RCT
	Setting	26 GPs in 13 towns in the United Kingdom; patients from 1 GP in each town were randomized to the intervention group
	Age and sex of participants	40–59 years; men and women
	Country	United Kingdom
	Date of study	No information provided

Table A4.1 contd

Study, start year: status	Data category	Description
	Diagnostic tests used	An interview recorded demographic details, medical history, family history and smoking habit, knowledge of CVD risk factors and perceived health. Measurements included height and weight, waist–hip ratio, exhaled breath carbon monoxide, blood pressure, and random total blood cholesterol and glucose levels in a capillary blood sample. Calculation of the Dundee risk score (103)
	Intervention	Family health checks conducted by nurses, including counselling and referral to GPs
	Total study duration	1-year follow-up
	Number of participants allocated to each arm	12 472 men aged 40–59 years and their partners (7460 men and 5012 women): intervention group, 2984; control group (internal and external), 9488
	Loss to follow-up for each outcome	73% of the target population participated in the health check; of these, follow-up was available for 85%
	Baseline comparability	No information provided
	Relevant outcomes	Prescription of medications (new medication)
	Results	No difference after 1 year in the prescription of medications (antihypertensive, lipid-lowering and antidiabetic). No numerical results were presented
Gothenburg, 1963 (31): completed	Study design	Parallel-group RCT
	Setting	Gothenburg, Sweden
	Age and sex of participants	50 years at study initiation; men
	Country	Sweden
	Date of study	Baseline data collected in 1963

Table A4.1 contd

Study, start year: status	Data category	Description
	Diagnostic tests used	Questionnaire and extensive health examination (e.g. blood pressure, BMI, lipid profile). Later examinations also included a physical test at maximum load
	Intervention	Repeated health examinations in 1963, 1967, 1973 and 1980 and referral to relevant treatment
	Total study duration	15-year follow-up
	Number of participants allocated to each arm	Intervention group, 1013; control group, 1967
	Loss to follow-up for each outcome	By the end of 1977: intervention group, 0.3%; control group, 1%
	Baseline comparability	Not assessed: the control group was not contacted at baseline
	Relevant outcomes	Total mortality, CVD mortality
	Results (intervention group vs control group)	Total mortality: 14.5% vs 15.6% ($\chi^2 = 0.35$) CVD mortality: 7.3% vs 6.7% ($\chi^2 = 0.72$) No differences were statistically significant
Gothenburg, 1970 (32): completed	Study design	Parallel-group RCT
	Setting	Gothenburg, Sweden
	Age and sex of participants	47–55 years at study initiation; men
	Country	Sweden
	Date of study	Baseline data collected between 1970 and 1973
	Diagnostic tests used	Questionnaire and screening examination collected data on weight, height, total serum cholesterol and blood pressure; and an ECG

Table A4.1 contd

Study, start year: status	Data category	Description
	Intervention	Screening examination at baseline and after 4 and 10 years. Treatment of risk factors: smoking (smoking cessation course), high blood pressure (medical treatment) and high cholesterol (dietary advice). Organized in special clinics. Individuals with angina were referred to a cardiologist
	Total study duration	Mean: 11.8 years
	Number of participants allocated to each arm	Intervention group, 10 004; control group 1 (some examinations), 10 011; control group 2 (no examinations): 10 007
	Loss to follow-up for each outcome	0%
	Baseline comparability	Baseline comparison between the intervention group and 2% of control group 1: the control group had a slightly higher prevalence of chronic diseases and considerably more alcohol problems
	Relevant outcomes	Total mortality, IHD morbidity & mortality (combined), stroke morbidity & mortality (combined), IHD mortality, stroke mortality
	Results (no. of cases; intervention group vs control group 1 vs control group 2)	Total mortality: 1293 vs 1304 vs 1332 IHD morbidity & mortality: 837 vs 836 vs 861 Stroke morbidity & mortality: 211 vs 196 vs 220 IHD mortality: 462 vs 453 vs 470 Stroke mortality: 64 vs 72 vs 82 No differences were statistically significant
Inter99, 1999 (21,33–37): completed	Comment	The two control groups were pooled for the meta-analysis
	Study design	Parallel-group RCT
	Setting	11 municipalities in the western part of Copenhagen County
	Age and sex of participants	30–60 years; men and women

Table A4.1 contd

Study, start year: status	Data category	Description
	Country	Denmark
	Date of study	Baseline data collected between 1999 and 2001
	Diagnostic tests used	Comprehensive questionnaire (lifestyle, motivation to change lifestyle, symptoms, history of diseases, family history of diseases, psychosocial factors), physical measurements (ECG, blood pressure, height and weight, waist and hip circumference, spirometry), blood samples (total cholesterol, total lipid profile, HgbA1c) and a 2-hour oral glucose tolerance test. Total CVD risk was assessed with PRECARD (104)
	Intervention	The intervention group was invited for screening, risk assessment and lifestyle counselling. Those at high risk of IHD (according to predefined criteria) were offered 6 sessions of group-based lifestyle counselling on smoking cessation, diet and physical activity. Participants at high risk were re-invited after 1 and 3 years. After 5 years, all participants who were eligible at baseline were re-invited for final screening, individual counselling and a maintenance plan
	Total study duration	10 years
	Number of participants allocated to each arm	Intervention group, 11 629; control group: 47 987
	Loss to follow-up for each outcome	0%
	Baseline comparability	Significantly different age and sex distribution, which was expected because of the sampling procedure. Significantly more people in the control group were cohabiting and had a lower education level

Table A4.1 contd

Study, start year: status	Data category	Description
	Relevant outcomes	Total mortality, IHD morbidity & mortality (combined), stroke morbidity & mortality (combined), CVD morbidity & mortality (combined) New medication: use of psychotropic medication (at 4 years before and 5 years after the start of the study) Hospitalization due to psychiatric diagnoses (at 4 years before and 5 years after the start of the study)
	Results	Total mortality: HR = 1.00 (95% CI: 0.91–1.09) IHD morbidity & mortality: HR = 1.03 (95% CI: 0.94–1.13) Stroke morbidity & mortality: HR = 0.98 (95% CI: 0.87–1.11) CVD morbidity & mortality: HR = 1.01 (95% CI: 0.93–1.09) Use of antipsychotics, hypnotics/sedatives, antidepressants or anxiolytics: no statistically significant differences Hospital admissions (all psychiatric disorders): <ul style="list-style-type: none"> • short term: OR = 1.07 (95% CI: 0.88–1.29, SE = 0.10, $P = 0.49$) • long-term: OR = 1.00 (95% CI: 0.83–1.21, SE = 0.10, $P = 0.98$) • drift (difference between short- and long-term effects): OR = 0.94 (95% CI: 0.76–1.16, SE = 0.10, $P = 0.55$)
Malmö, 1969 (38,39): completed	Study design	Parallel-group RCT
	Setting	Malmö
	Age and sex of participants	55 years; men
	Country	Sweden
	Date of study	Baseline data collected in 1969
	Diagnostic tests used	Questionnaire and health examination: weight, blood pressure, lipid profile and lung function

Table A4.1 contd

Study, start year: status	Data category	Description
	Intervention	Examination focusing on cardiovascular and pulmonary function. If needed, participants were referred to specialists for follow-up
	Total study duration	1970–1974 (5 years)
	Number of participants allocated to each arm	Intervention group, 809; control group, 804
	Loss to follow-up for each outcome	1%
	Baseline comparability	No comparison made: the control group was not contacted at baseline
	Relevant outcomes	Total mortality, CVD mortality, hospitalization, receipt of a disability pension
	Results	Total mortality (participants vs non-participants vs control group): 7.5% vs 5.8% vs 7.5% (NSD) CVD mortality (participants & non-participants vs control group): 14 vs 33 cases, $\chi^2 = 9.09$, $P < 0.01$ Hospitalization (participants vs non-participants vs control group): 37.6% (total days: 6927) vs 29% (total days: 917) vs 35.6% (total days: 8501; NSD) Disability pension (participants vs non-participants vs control group): 6.6% vs 8.8% vs 9% (NSD)
Northumberland, 1969 (40): completed	Study design	Parallel-group RCT
	Setting	7 GPs in 4 general practices in the north of England
	Age and sex of participants	50–59 years; men
	Country	England, United Kingdom
	Date of study	Baseline data collected in 1969

Table A4.1 contd

Study, start year: status	Data category	Description
	Diagnostic tests used	Questionnaire and clinical examination (limited to the system(s) affected). Not specified in greater detail
	Intervention	Two intervention groups: 1 completed a questionnaire and was subsequently invited to attend their GP for further examination of symptoms declared in their answers; the other completed the questionnaire and underwent a full examination
	Total study duration	18 months
	Number of participants allocated to each arm	867 (59 were excluded due to severe illness/death or could not be traced): control (group 1), 291; less-intensive intervention (group 2), 275; full intervention (group 3), 242
	Loss to follow-up for each outcome	9.8%
	Baseline comparability	Group 1 contained a small excess of patients with previously diagnosed conditions; not statistically significant
	Relevant outcomes	Hospitalizations (≥ 1), number of physician visits/consultations, diagnostic procedures (examinations, investigations performed and presumptive diagnoses), new medication and certified sickness

Table A4.1 contd

Study, start year: status	Data category	Description
	Results (group 1 vs group 2 vs group 3)	<p>Hospitalizations (≥ 1): 6.1% vs 5.5% vs 4.2%; $P \leq 0.05$</p> <p>Number of physician visits/consultations:</p> <ul style="list-style-type: none"> • average number of consultations: 5.0 vs 5.2 vs 5.4 (NSD) • average number of new consultations: 1.4 vs 1.4 vs 1.5 (NSD) <p>Diagnostic procedures:</p> <ul style="list-style-type: none"> • physical examination: 63.7% vs 65.4% vs 68.6% ($P \leq 0.01$) • laboratory investigation: 4.5% vs 5.4% vs 8.8% ($P \leq 0.001$) • presumptive diagnosis: 80.8% vs 79.8% vs 80.9% (NSD) <p>New medication: 50.9% vs 48.7% vs 53.1% (NSD)</p> <p>Certified sickness:</p> <ul style="list-style-type: none"> • 1–14 days: 40.4% vs 42.1% vs 36.2% (NSD) • ≥ 15 days: 4.7% vs 5.8% vs 6.9% ($P \leq 0.05$; significantly more in group 3)
South-East London, 1967 (41): completed	Study design	Cluster RCT
	Setting	2 GPs in South-east London
	Age and sex of participants	40–64 years; men and women plus their families
	Country	England, United Kingdom
	Date of study	Baseline data collected in 1967–1968
	Diagnostic tests used	Questionnaire and clinical tests (anthropometry, visual testing, audiometry, chest X-ray, lung function test, ECG, blood pressure, blood tests (including cholesterol and blood sugar), stool sample and basic physician examination)
	Intervention	Two screening sessions about 2 years apart. Counselling and referral to GPs
	Total study duration	9 years

Table A4.1 contd

Study, start year: status	Data category	Description
	Number of participants allocated to each arm	Intervention group, 3867; control group, 3353
	Loss to follow-up for each outcome	Varied for different outcomes: 26.6–34.5%
	Baseline comparability	No significant differences between groups
	Relevant outcomes	After 8 years: total mortality, CVD mortality, hospitalizations, physician visits/consultations, certified sickness
	Results (intervention group vs control group)	<p>Total mortality (per 1000 person-years at risk): 10.0 vs 9.2 CVD mortality (per 1000 person-years at risk): 4.3 vs 2.8 Hospitalizations (total admissions per 1000 person-years at risk): 73.4 vs 70.7 GP visits/consultations (overall consultation rate):</p> <ul style="list-style-type: none"> • men: 3.2 (SE = 0.09) vs 3.1 (SE = 0.09) • women: 4.0 (SE = 0.09) vs 3.8 (SE = 0.09) <p>Certified sickness: participants in both groups lost 5.5% of their work time to certified sickness absence No differences were statistically significant</p>
Stockholm, 1969 (42): completed	Study design	Parallel-group RCT
	Setting	Stockholm, Sweden
	Age and sex of participants	18–65 years; men and women
	Country	Sweden
	Date of study	Baseline data collected in 1969–1970
	Diagnostic tests used	Screening included social, psychiatric and medical interviews; blood pressure and blood tests; physical examinations, ECGs, exercise tests, psychological tests, and eye and dental examinations

Table A4.1 contd

Study, start year: status	Data category	Description
	Intervention	Extensive general health and social screening, focusing primarily on function. The examinations were done by social workers, psychiatrists and physicians during a single day. If needed, participants were referred for specialist treatment. Simple health-care services were provided by the intervention providers
	Total study duration	22 years
	Number of participants allocated to each arm	Intervention group, 3064; control group, 29 122
	Loss to follow-up for each outcome	1%
	Baseline comparability	No comparison made: baseline data were not collected for the control group
	Relevant outcomes	Total mortality, CVD mortality
	Results	Total mortality: rate ratio = 1.03 (95% CI: 0.94–1.14) CVD mortality: rate ratio = 1.06 (95% CI: 0.88–1.23)
Check your Health, 2013 (43): ongoing	Study design	Cluster RCT
	Setting	A selected geographical area in the Central Denmark Region
	Age and sex of participants	30–49 years; men and women
	Country	Denmark
	Date of study	Baseline data collected in 2013–2014

Table A4.1 contd

Study, start year: status	Data category	Description
	Diagnostic tests used	Questionnaire and clinical tests: blood pressure; BMI; HbA1c and lipid profile (total cholesterol, HDL, LDL, triglycerides); height, weight and waist measurements; lung function/spirometry; physical fitness. Risk of CVD within 10 years was calculated using SCORE (105)
	Number of participants	Total, 10 505
	Intervention	Preventive health checks and assignment of individual risk profile. Based on the risk profile, participants are referred to 1 of 3 programmes: health promotion consultation with GP, behavioural programme at local health centre or no need for follow-up
	Total study duration	Primary outcomes at 4-year follow-up
	Relevant outcomes	Risk of cardiovascular event (Heart-SCORE model (105)), sick leave, labour market attachment, cost-effectiveness
Gadchiroli, 2016 (44): ongoing	Study design	Cluster RCT
	Setting	32 rural villages in Gadchiroli
	Age and sex of participants	≥ 50 years; men and women
	Country	India
	Date of study	Baseline data collected in 2016
	Diagnostic tests used	Blood pressure, urine glucose test; measurement of weight, height, and waist and hip circumference
	Number of participants	Not specified
	Intervention	Intervention group will be screened by community health workers for diabetes, hypertension and stroke, followed up with treatment and home visits



Table A4.1 contd

Study, start year: status	Data category	Description
	Total study duration	Planned duration of the intervention, 3.5 years; primary outcome collected after 2.5 years
	Relevant outcomes	Stroke mortality, all-cause and cardiovascular mortality, percentage of hypertensive patients taking blood pressure medications, blood pressure control, blood glucose control

BMI: body mass index; CI: confidence interval; ECG: electrocardiogram; GP: general practitioner; HbA_{1c}: glycated haemoglobin; HDL: high-density lipoprotein; HR: hazard ratio; Inter99: A Randomised Non-pharmacological Intervention Study for Prevention of Ischaemic Heart Disease Inter99; LDL: low-density lipoprotein; NSD: not significantly different; OR: odds ratio; SE: standard error.

^a No information given on when the baseline data were collected.

Table A4.2. Data extracted from included studies on screening for AAA

Study, start year: status	Data category	Description
Chichester, 1989 (45–47): completed	Study design	Parallel-group RCT
	Setting	9 GPs in the Chichester district
	Age and sex of participants	65–80 years; men
	Country	England, United Kingdom
	Date of study	Baseline data collected in 1989
	Diagnostic tests used	Abdominal ultrasonographic screening
	Intervention	AAA was considered present if the aortic diameter was > 3 cm. Participants with an aortic diameter of 3.0–4 cm were rescanned annually, and those with an aortic diameter of 4.5–5.9 cm were scanned every 3 months. Participants with an aortic diameter of > 6 cm, rapid expansion of ≥ 1 cm per year or symptoms related to AAA were referred for surgical evaluation
	Total study duration	15-year follow-up
	Number of participants allocated to each arm	Intervention group, 2995; control group, 3045
	Loss to follow-up for each outcome	0%
	Baseline comparability	No comparison made: baseline data were not collected for the control group
	Relevant outcomes	AAA mortality, AAA rupture, total mortality
	Results	AAA mortality: HR = 0.89 (95% CI: 0.60–1.32) AAA rupture: HR = 0.88 (95% CI: 0.61–1.26) Total mortality: HR = 1.01 (95% CI: 0.95–1.07)

Table A4.2 contd

Study, start year: status	Data category	Description
Chichester, 1989 (45–47): completed	Study design	Parallel-group RCT
	Setting	9 GPs in the Chichester district
	Age and sex of participants	65–80 years; women
	Country	England, United Kingdom
	Date of study	Baseline data collected in 1989
	Diagnostic tests used	Abdominal ultrasonographic screening
	Intervention	AAA was considered present if the aortic diameter was > 3 cm. Participants with an aortic diameter of 3.0–4 cm were rescanned annually, and those with an aortic diameter of 4.5–5.9 cm were scanned every 3 months. Participants with an aortic diameter of > 6cm, rapid expansion of ≥ 1 cm per year or symptoms related to AAA were referred for surgical evaluation
	Total study duration	5- and 10-year follow-up
	Number of participants allocated to each arm	Intervention group, 4682; control group, 4660
	Loss to follow-up for each outcome	0%
	Baseline comparability	No comparison made: baseline data were not collected for the control group
	Relevant outcomes	AAA mortality, AAA rupture, total mortality
	Results (intervention group vs control group)	<p>AAA mortality (5 years): 3 cases vs 2 cases</p> <p>AAA rupture:</p> <ul style="list-style-type: none"> incidence at 5 years: 3 cases vs 2 cases incidence at 10 years: 14 cases vs 9 cases <p>Total mortality (5 years): 10.7% vs 10.2%</p>

Table A4.2 contd

Study, start year: status	Data category	Description
Multicentre Aneurysm Screening Study, 1997 (48): completed	Study design	Parallel-group RCT
	Setting	4 centres in the United Kingdom
	Age and sex of participants	65–74 years; men
	Country	United Kingdom
	Date of study	Baseline data collected in 1997–1999
	Diagnostic tests used	Abdominal ultrasonographic screening
	Intervention	Patients with AAA (aortic diameter of ≥ 3 cm) were kept under surveillance and offered surgery after predefined criteria had been met. When the aortic diameter reached 5.5 cm, aortic expansion was ≥ 1 cm in 1 year, or patients reported symptoms attributable to AAA, patients were referred for surgical evaluation
	Total study duration	Follow-up was 8.9–11.2 years (mean: 10.1)
	Number of participants allocated to each arm	Intervention group, 33 883; control group, 33 887
	Loss to follow-up for each outcome	Mortality at 10 years, 2.7%; for clinical follow-up (e.g. non-fatal AAA rupture), 28%
	Baseline comparability	The randomized groups were well balanced in terms of age, geographical area and socioeconomic status (106)
	Relevant outcomes	AAA mortality, AAA rupture, total mortality, costs

Table A4.2 contd

Study, start year: status	Data category	Description
	Results	AAA mortality: HR = 0.52 (95% CI: 0.43–0.63) AAA rupture: HR = 0.52 (95% CI: 0.44–0.62) Total mortality: HR = 0.97 (95% CI: 0.95–1.00) Regarding AAA-related mortality, the incremental cost per man invited to screening was £100 (95% CI: 82–118), leading to an incremental cost-effectiveness ratio of £7600 (95% CI: 5100–13 000) per life-year gained.
Viborg, 1994 (49): completed	Study design	Parallel-group RCT
	Setting	Viborg County
	Age and sex of participants	64–73 years; men
	Country	Denmark
	Date of study	Baseline data collected in 1994. From 1995 to 1998, all men who turned 65 years were included
	Diagnostic tests used	Abdominal ultrasonographic screening
	Intervention	AAA was considered present if the aortic diameter was ≥ 3 cm. Participants with an aortic diameter of ≥ 5 cm were referred to a vascular surgeon. Participants with an aortic diameter of 3–4.99 cm were offered annual ultrasonography
	Total study duration	Mean: 13 years (SD = 1.3)
	Number of participants allocated to each arm	Intervention group, 6333; control group, 6306
	Loss to follow-up for each outcome	0%

Table A4.2 contd

Study, start year: status	Data category	Description
Western Australia, 1996 (50): completed	Baseline comparability	Groups were similar for duration of observation and age (107)
	Relevant outcomes	AAA mortality, total mortality, costs
	Results	AAA mortality: HR = 0.34 (95% CI: 0.20–0.57) Total mortality: HR = 0.98 (95% CI: 0.93–1.03) Regarding total mortality, the ICER was estimated at €157 (95% CI: –3292 to 4401) per life-year gained and €179 (95% CI: –4083 to 4682) per quality-adjusted life-year gained
	Study design	Parallel-group RCT
	Setting	Perth, Western Australia
	Age and sex of participants	64–83 years; men (planned subgroup analysis of men aged 65–74 years)
	Country	Australia
	Date of study	Baseline data collected in 1996–1999
	Diagnostic tests used	Abdominal ultrasonographic screening
	Intervention ^a	Participants were screened for AAA at 5 community-based clinics. Participants and GPs were informed about the results of the scan. GPs arranged follow-up or referred participants to a surgeon. No general guidelines for management were given
	Total study duration	Mean of 12.8 years (range: 11.6–14.2)
	Number of participants allocated to each arm	Intervention group, 19 249; control group, 19 231
	Loss to follow-up for each outcome	0%

Table A4.2 contd

Study, start year: status	Data category	Description
	Baseline comparability	No comparison made: baseline data were not collected for the control group
	Relevant outcomes	AAA mortality, total mortality
	Results	<p>AAA mortality:</p> <ul style="list-style-type: none"> • men aged 64–83 years: HR = 0.91 (95% CI: 0.68–1.21) • men aged 65–74 years: HR = 0.92 (95% CI: 0.62–1.36) <p>Total mortality:</p> <ul style="list-style-type: none"> • men aged 64–83 years: HR = 0.98 (95% CI: 0.96–1.01) • men aged 65–74 years: HR = 0.99 (95% CI: 0.95–1.02)

CI: confidence interval; GP: general practitioner; HR: hazard ratio; ICER: incremental cost–effectiveness ratio; SD: standard deviation.

^a Despite a more uncertain handling of persons with an aortic diameter of > 3 cm, there were no fewer elective surgeries in this study than in the Viborg study (49) and Multicentre Aneurysm Screening Study (48).

Table A4.3. Data extracted from included studies on screening for AF

Study, start year: status	Data category	Description
STROKESTOP, 2012 (51): ongoing	Study design	Parallel-group RCT
	Setting	Two Swedish regions
	Age and sex of participants	75–76 years; men and women
	Country	Sweden
	Date of study	2012
	Diagnostic tests used	Intermittent ECG recording
	Number of participants	13 331 have been invited; 7173 have participated
	Intervention	Screening for AF and follow-up with oral anticoagulant treatment
	Total study duration	5 years of follow-up
	Relevant outcomes	Incidence of ischaemic stroke, thromboembolic event, intracranial bleeding, other major bleeding, first ever diagnosis of dementia, death from any cause, and a composite of all outcomes

Table A4.3 contd

Study, start year: status	Data category	Description
VITAL-AF, 2018 (52): ongoing	Study design	Cluster RCT
	Setting	22 GPs, Massachusetts
	Age and sex of participants	65 years or older; men and women
	Country	United States of America
	Date of study	Enrolment began in 2018
	Diagnostic tests used	Single-lead handheld ECG
	Number of participants	Estimated 16 000 participants in each arm
	Intervention	Screening for AF and follow-up at the participant's GP
	Total study duration	Primary outcomes after 12 months, secondary outcomes after 24 months
	Relevant outcomes	Incident AF (12 months), new oral anticoagulation drug prescriptions (12 months), continued use of oral anticoagulation drugs (24 months), incident ischaemic stroke (24 months), major haemorrhage (24 months)

ECG: electrocardiogram; GP: general practitioner; STROKESTOP: Systematic ECG Screening for Atrial Fibrillation Among 75 Year Old Subjects in the Region of Stockholm and Halland, Sweden; VITAL-AF: Full title: Screening for Atrial Fibrillation in an Ambulatory Clinic Population: the VITAL-AF Study.

Table A4.4. Data extracted from included studies on combined screening for preclinical CVDs

Study, start year: status	Data category	Description
Viborg Vascular, 2008 (53): completed	Study design	RCT
	Setting	Viborg, Central Denmark Region
	Age and sex of participants	65–74 years, men
	Country	Denmark
	Date of study	Baseline data collected between 2008 and 2011
	Diagnostic tests used	Portable ultrasound scanner, bedside equipment for cholesterol measurement, portable Doppler, blood pressure measurement
	Intervention	Screening for AAA, hypertension and PAD, followed by pharmacological therapy and surgical repair (only for AAA). Participants with detected hypertension were referred to their GP
	Total study duration	5-year follow-up (median: 4.4 years)
	Number of participants allocated to each arm	Intervention group, 25 078; control group, 25 078
	Loss to follow-up for each outcome	4 participants (<1%)
	Baseline comparability	No differences were noted in baseline characteristics
	Relevant outcomes	Total mortality, CVD mortality, AAA-related mortality, hospital admission due to CVD, AAA progression, adverse effects of cancer, diabetes, intracerebral haemorrhage and renal failure

Table A4.4 contd

Study, start year: status	Data category	Description
	Results	Total mortality: HR = 0.93 (95% CI: 0.88–0.98; $P = 0.01$) CVD mortality: HR = 0.93 (95% CI: 0.86–1.02; NSD) AAA-related mortality: HR = 0.62 (95% CI: 0.38–1.02; NSD) Cancer-related mortality: HR = 0.97 (95% CI: 0.91–1.04; NSD) Other cause-related mortality: HR = 0.93 (95% CI: 0.81–1.06; NSD) Unknown cause mortality: HR = 0.87 (95% CI: 0.73–1.03; NSD) Hospital admission due to CVD (composite outcome): NSD
DANCAVAS, 2014 (54): ongoing	Study design	RCT
	Setting	Island of Funen, or surrounding communities of Vejle and Silkeborg
	Age and sex of participants	65–74 years, men
	Country	Denmark
	Date of study	Enrolment initiated in 2014
	Diagnostic tests used	Low-dose non-contrast computed tomography scan, brachial and ankle blood pressure index, telemetric assessment of heart rhythm, and measurements of cholesterol and plasma glucose levels
	Number of participants	45 000
	Intervention	Screening followed by cardiovascular preventive treatment in case of positive findings
	Total study duration	10 years
	Relevant outcomes	Total mortality; costs after 3, 5 and 10 years

CI: confidence interval; DANCAVAS: Danish Cardiovascular Screening Trial II;
GP: general practitioner; HR: hazard ratio; NSD: not significantly different.

ANNEX 5. DETAILED RESULTS OF THE META-ANALYSES

Meta-analyses were conducted to analyse comparable data on specific outcomes, where available in the included studies. Where available, the formal name of each RCT is given; where not, the geographical location is given. NB: references are given in the main reference list.

Screening for CVD risk and CVD risk factors

A total of nine studies reported the specific outcomes of RCTs on screening CVD risk and CVD risk factors (21,23,24,29,31,32,38,41,42). Some studies reported a combined outcome for morbidity and mortality, as well as a separate outcome for mortality. Therefore, separate meta-analyses were conducted for the mortality and combined morbidity/mortality outcomes.

Total mortality

All nine studies reported on total mortality, with follow-up ranging from five to 30 years (21,23,24,29,31,32,38,41,42). All reported no reduction in total mortality following screening for CVD risk and CVD risk factors. This finding was confirmed by the meta-analysis, which determined an overall relative risk for total mortality of 1.00 (95% CI: 0.97–1.03; Table A5.1).

A low level of heterogeneity across all nine studies indicated that they had produced similar results. Sensitivity analyses of the risk of bias did not alter the overall results, confirming that the analysis was robust. The inclusion of adjusted results (hazard ratios) instead of the absolute number of cases did not change the results.

CVD morbidity and mortality

The two studies that reported on CVD morbidity and mortality (combined) had follow-up periods of 10 and 24 years (21,24). Both reported no reductions in CVD morbidity and mortality following screening for CVD risk and CVD risk factors. This finding was confirmed in the meta-analysis, which determined an overall relative risk for CVD morbidity and mortality of 1.02 (95% CI: 0.95–1.10; Table A5.2).

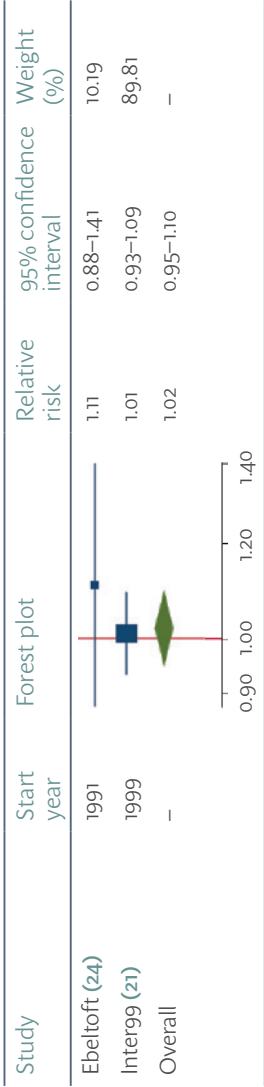
A low level of heterogeneity across the two studies indicated that they had produced similar results. Sensitivity analyses of the risk of bias did not alter the overall effect estimate, which strengthened confidence in the meta-analysis.

Table A5.1. Screening for CVD risk/risk factors: meta-analysis of total mortality outcomes

Study	Start year	Forest plot	Relative risk	95% confidence interval	Weight (%)
Gothenburg (31)	1963		0.94	0.78–1.13	3.31
South-East London (41)	1967		1.10	0.90–1.35	2.74
Erfurt-Süd (29)	1968		0.97	0.66–1.42	0.75
Malmö (38)	1969		0.81	0.56–1.17	0.82
Stockholm (42)	1969		1.03	0.94–1.13	11.60
Gothenburg (32)	1970		0.98	0.92–1.04	27.41
DanMONICA (23)	1982		1.03	0.98–1.09	36.82
Ebeltoft (24)	1991		0.93	0.75–1.16	2.30
Inter99 (21)	1999		0.96	0.88–1.04	14.26
Overall	–		1.00	0.97–1.03	–

Notes: random effects restricted maximum likelihood model.
A relative risk of < 1 favours screening; a relative risk of > 1 favours the control.
Heterogeneity statistics: $I^2 = 0.00$, $P = 1.31\%$, $H^2 = 1.01$.
Test of $\theta_1 = 0$; $Q(8) = 6.00$, $P = 0.65$.
Test of $\theta = 0$: $z = -0.01$, $P = 0.99$.

Table A5.2. Screening for CVD risk/risk factors: meta-analysis of CVD morbidity and mortality



Notes: random effects restricted maximum likelihood model.
A relative risk of < 1 favours screening; a relative risk of > 1 favours the control.
Heterogeneity statistics: $\tau^2 = 0.00$, $I^2 = 1.01\%$, $H^2 = 1.00$.
Test of $\theta_1 = \theta_j$: $Q(1) = 0.55$, $P = 0.46$.
Test of $\theta = 0$: $z = 0.51$, $P = 0.61$.

CVD mortality

The five studies that reported on CVD mortality had follow-up ranging from five to 22 years (29,31,38,41,42). The study with the shortest follow-up reported a reduction in CVD mortality among participants in the screened group after five years (38). The other four studies reported no reductions in CVD mortality (29,31,41,42). The latter finding was confirmed in the meta-analysis, which determined an overall relative risk of CVD mortality of 1.04 (95% CI: 0.73–1.49; Table A5.3).

Substantial heterogeneity across the studies indicated that they had not produced similar results. Sensitivity analyses of the risk of bias did not alter the overall effect estimate, which strengthened confidence in the meta-analysis.

Table A5.3. Screening for CVD risk/risk factors: meta-analysis of CVD mortality

Study	Start year	Forest plot	Relative risk	95% confidence interval	Weight (%)
Gothenburg (31)	1963		1.09	0.83–1.43	23.11
Erfurt-Süd (29)	1968		1.30	0.71–2.37	15.26
Malmö (38)	1969		0.42	0.23–0.78	14.90
South-East London (41)	1967		1.54	1.09–2.16	21.48
Stockholm (42)	1969		1.06	0.90–1.25	25.25
Overall	–		1.04	0.73–1.49	–

Notes: random effects restricted maximum likelihood model.

A relative risk of < 1 favours screening; a relative risk of > 1 favours the control.

Heterogeneity statistics: $t^2 = 0.13$, $I^2 = 82.20\%$, $H^2 = 5.62$.

Test of $\theta_1 = \theta_j$: $Q(4) = 13.39$, $P = 0.01$.






Test of $\theta = 0$: $z = 0.20$, $P = 0.84$.

IHD morbidity and mortality

A total of four studies reported on IHD morbidity and mortality (combined (21,23,29,32), with follow-up ranging from around nine to 30 years. All four studies reported no reduction in IHD morbidity and mortality following screening for CVD risk and CVD risk factors. This finding was confirmed by the meta-analysis, which determined an overall relative risk for IHD morbidity and mortality of 1.00 (95% CI: 0.96–1.05; Table A5.4).

A low level of heterogeneity across all four studies indicated that they had produced similar results. Sensitivity analyses of the risk of bias did not alter the overall results, which strengthened confidence in the meta-analysis.

Table A5.4. Screening for CVD risk/risk factors: meta-analysis of IHD morbidity and mortality

Study	Start year	Forest plot	Relative risk	95% confidence interval	Weight (%)
Erfurt-Süd (29)	1968		1.36	0.90–2.06	1.29
Göteborg (32)	1970		0.99	0.91–1.07	34.74
DanMONICA (23)	1982		0.99	0.92–1.07	38.23
Inter99 (21)	1999		1.03	0.94–1.13	25.74
Overall	–		1.00	0.96–1.05	–

Notes: random effects restricted maximum likelihood model.

A relative risk of < 1 favours screening; a relative risk of > 1 favours the control.

Heterogeneity statistics: $\tau^2 = 0.00$, $I^2 = 0.02\%$, $H^2 = 1.00$.

Test of $\theta_1 = \theta_j$: $Q(3) = 2.74$, $P = 0.43$.

Test of $\theta = 0$: $z = 0.13$, $P = 0.89$.



IHD mortality

In all, two studies reported outcomes for IHD mortality, with follow-up ranging from 9 to 11.8 years (29,32). Both studies reported no reductions in IHD mortality following screening for CVD risk and CVD risk factors. This finding was confirmed in the meta-analysis, which determined an overall relative risk for IHD mortality of 1.00 (95% CI: 0.90–1.12; Table A5.5).

A low level of heterogeneity across both studies indicated that they had produced similar results. Sensitivity analyses of the risk of bias did not alter the overall effect estimate, which strengthened confidence in the meta-analysis.

Table A5.5. Screening for CVD risk/risk factors: meta-analysis of IHD mortality

Study	Study year	Forest plot	Relative risk	95% confidence interval	Weight (%)
Erfurt-Süd (29)	1968		1.09	0.54–2.19	2.40
Gothenburg (32)	1970		1.00	0.90–1.12	97.60
Overall	–		1.00	0.90–1.12	–

0.60 1.00 1.50 2.00

Notes: random effects restricted maximum likelihood model.
A relative risk of < 1 favours screening; a relative risk of > 1 favours the control.
Heterogeneity statistics: $t^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$.
Test of $\theta_i = \theta_j$: $Q(1) = 0.06$, $P = 0.81$.
Test of $\theta = 0$: $z = 0.07$, $P = 0.95$.

Stroke morbidity and mortality

Three studies reported on stroke morbidity and mortality (combined) (21,23,32). Two studies, with follow-up of 10 and 11.8 years, reported no reductions in this outcome following screening for CVD risk and CVD risk factors (21,32). The third study, which had follow-up of around 30 years, reported an increased risk of stroke in the screened group (23). The meta-analysis found an overall relative risk for stroke morbidity and mortality of 1.05 (95% CI: 0.95–1.17), indicating no difference in the risk of stroke following screening for CVD risk and CVD risk factors (Table A5.6).

Moderate heterogeneity across all three studies indicated that they had not produced similar results. Sensitivity analyses of the risk of bias did not alter the overall effect estimate, which strengthened confidence in the meta-analysis.

Table A5.6. Screening for CVD risk/risk factors: meta-analysis of stroke morbidity and mortality

Study	Study year	Forest plot	Relative risk	95% confidence interval	Weight (%)
Gothenburg (32)	1970		1.01	0.86–1.20	24.25
DanMONICA (23)	1982		1.14	1.04–1.25	42.17
Inter99 (21)	1999		0.98	0.87–1.11	33.57
Overall	–		1.05	0.95–1.17	–

Notes: random effects restricted maximum likelihood model.

A relative risk of < 1 favours screening; a relative risk of > 1 favours the control.

Heterogeneity statistics: $t^2 = 0.00$, $I^2 = 52.35\%$, $H^2 = 2.10$.

Test of $\theta_1 = \theta_2$: $Q(2) = 4.22$, $P = 0.12$.

Test of $\theta = 0$: $z = 1.00$, $P = 0.32$.



Stroke mortality

Only one study reported on screening for CVD risk and CVD risk factors. It found that screening did not lead to a reduction in stroke mortality after 11.8 years of follow-up (32).

Screening for AAA

A total of four studies reported the specific outcomes of RCTs on screening for AAA (45,48–50).

Total mortality

All four studies reported total mortality for men, with follow-up ranging from 10 to 15 years (45,48–50). None of the studies reported a reduction in total mortality following screening. This finding was confirmed in the meta-analysis, which determined an overall relative risk for total mortality of 0.99 (95% CI: 0.98–1.00; Table A5.7). Only one study reported total mortality for women: it found no reduction at five years after screening (46).

Table A5.7. Screening for AAA: meta-analysis of total mortality

Study	Start year	Forest plot	Relative risk	95% confidence interval	Weight (%)
Chichester (45)	1989		1.00	0.97–1.04	13.79
Viborg (49)	1994		0.98	0.95–1.02	11.91
Western Australia (50)	1996		0.99	0.97–1.01	42.07
MASS (48)	1997		0.98	0.96–1.00	32.23
Overall	–		0.99	0.98–1.00	–

0.95 1.00 1.05

MASS: Multicentre Aneurysm Screening Study.

Notes: random effects restricted maximum likelihood model.

A relative risk of < 1 favours screening; a relative risk of > 1 favours the control.

Heterogeneity statistics: $\tau^2 = 0.00$, $I^2 = 0.04\%$, $H^2 = 1.00$.

Test of $\theta_1 = \theta_2$: $Q(3) = 1.12$, $P = 0.77$.

Test of $\theta = 0$: $z = -1.85$, $P = 0.07$.






A low level of heterogeneity across studies indicated that they had produced similar results. Sensitivity analyses of the risk of bias did not alter the overall effect estimate, which strengthened confidence in the meta-analysis. However, the inclusion of adjusted results (hazard ratios) instead of the absolute number of cases showed a 2% reduction in total mortality (relative risk: 0.98; 95% CI: 0.96–0.99; Table A5.8).

AAA mortality

All four RCTs reported AAA mortality for men, with follow-up ranging from 10 to 15 years (45,48–50). Two of the studies reported reductions in AAA mortality following screening (48,49), whereas the other two reported no reductions (45,50). The meta-analysis showed that screening reduces AAA mortality, with an overall relative risk of 0.63 (95% CI: 0.41–0.97; Table A5.1). The only identified study to report findings for women found no reduction in AAA mortality at five years after screening (46).

Substantial heterogeneity across studies indicated that they had not produced similar results. Sensitivity analyses of the risk of bias did not alter the overall effect estimate, which strengthened confidence in the meta-analysis. Furthermore,

Table A5.8. Screening for AAA: meta-analysis of AAA mortality

Study	Start year	Forest plot	Relative risk	95% confidence interval	Weight (%)
Chichester (45)	1989		0.88	0.60–1.30	24.16
Viborg (49)	1994		0.34	0.20–0.58	20.83
Western Australia (50)	1996		0.92	0.69–1.22	26.59
MASS (48)	1997		0.52	0.43–0.64	28.42
Overall	–		0.63	0.41–0.97	–

0.25 0.40 0.65 1.00 1.50 2.50

MASS: Multicentre Aneurysm Screening Study.

Notes: random effects restricted maximum likelihood model.

A relative risk of < 1 favours screening; a relative risk of > 1 favours the control.

Heterogeneity statistics: $\tau^2 = 0.16$, $I^2 = 86.00\%$, $H^2 = 7.14$.

Test of $\theta_1 = \theta_j$: $Q(3) = 18.30$, $P = 0.00$.

Test of $\theta = 0$: $z = -2.11$, $P = 0.04$.



the inclusion of adjusted results (hazard ratios) instead of the absolute number of cases did not change the results.

AAA rupture

Two studies reported AAA rupture for men (45,48): one study reported no reduction in AAA rupture after 15 years (45), whereas the other reported a relative risk reduction of almost 50% in the screened group after 10 years (48). The meta-analysis showed that screening does not reduce AAA rupture, with an overall relative risk of 0.66 (95% CI: 0.40–1.09). The only identified study to report findings for women found no reduction in the AAA rupture rate at five and 10 years after screening (47).

Substantial heterogeneity across studies indicated that they had not produced similar results. Sensitivity analyses of the risk of bias did not alter the overall effect estimate, which strengthened confidence in the meta-analysis. Furthermore, the inclusion of adjusted results (hazard ratios) instead of the absolute number of cases did not change the results.

Table A5.9. Screening for AAA: meta-analysis of AAA rupture

Study	Start year	Forest plot	Relative risk	95% confidence interval	Weight (%)
Chichester (45)	1989		0.88	0.61–1.26	44.96
MASS (48)	1997		0.53	0.44–0.63	55.04
Overall	–		0.66	0.40–1.09	–

MASS: Multicentre Aneurysm Screening Study.

Notes: random effects restricted maximum likelihood model.

A relative risk of < 1 favours screening; a relative risk of > 1 favours the control.

Heterogeneity statistics: $t^2 = 0.11$, $I^2 = 84.07\%$, $H^2 = 6.28$.

Test of $\theta_1 = \theta_j$: $Q(1) = 6.28$, $P = 0.01$.

Test of $\theta = 0$: $z = -1.61$, $P = 0.11$.

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