UK National Screening Committee

Screening for cardiac conditions associated with sudden cardiac death in the young

External review against programme appraisal criteria for the UK National Screening Committee

Version: FINAL

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The UK National Screening Committee secretariat is hosted by Public Health England.

About the UK National Screening Committee (UK NSC)

The UK NSC advises ministers and the NHS in the 4 UK countries about all aspects of population screening and supports implementation of screening programmes. Conditions are reviewed against evidence review criteria according to the UK NSC's evidence review process.

Read a complete list of UK NSC recommendations.

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Plain English summary

Sudden cardiac death (SCD) is the sudden and unexpected death of a person, caused by a problem with their heart. A number of conditions can cause SCD. In people under 35 years, SCD is often caused by a thickening of the heart muscle (cardiomyopathy) or an electrical problem with the heart (for example, long QT syndrome). As people get older, SCD is more likely to be caused by narrowing of the blood vessels that supply the heart (coronary artery disease).

Screening has been proposed by some people as a way to prevent sudden cardiac death in young people (12-39 years). The way this might work is by identifying heart conditions at an early stage before they cause symptoms. This would allow treatment to start earlier, which might prevent SCD. Other people think that screening would not be effective and may cause harm through unnecessary tests and treatments.

Common ways to identify these conditions include:

- asking individuals about specific symptoms and family history (medical history)
- recording blood pressure, pulses, and listening to the heart (physical examination)
- recording an electrical tracing of the heart (electrocardiogram)

The UK National Screening Committee (UK NSC) last looked at the evidence for screening for SCD in the young in 2014. The report concluded that there was not enough evidence to support screening. This was because:

- there were uncertainties on how many young people each year were affected by sudden cardiac death
- it was unclear whether the tests could accurately detect heart conditions in young people without symptoms
- there was no research that testing young people reduced the chance of a sudden cardiac death

This evidence summary updates the previous UK NSC review and examines all new evidence published since 2014. The focus of this review is on screening of individuals in the general population without symptoms. It does not consider the role of screening in special groups, such as athletes or individuals with symptoms.

The main conclusions of this review are:

- sudden cardiac death is an important health condition

- research shows that current tests are not accurate enough to use in young people without symptoms
- there was no research showing that screening reduces the chance of a sudden cardiac death in the general population

Therefore, the UK NSC still cannot recommend population screening for sudden cardiac death in the young. Further research is necessary to understand whether screening is effective. However, before researchers can do a research trial of screening, there is a need for accurate screening tests and clear guidelines to enable clinicians to treat patients that have a disease, but do not have symptoms.

Executive summary

Purpose of the review

This rapid review on sudden cardiac death (SCD) in the young provides an update to the previous UK National Screening Committee (UK NSC) review published in 2014. The current review assesses the quality and volume of evidence published since 2014 on the incidence of SCD (since 2008 for UK studies), on the accuracy of screening tests and on the effectiveness of screening.

Background

Sudden cardiac death describes the unexpected death of an individual due to a cardiac cause where the death occurs soon after symptoms start (within one hour) or they are found dead having had no symptoms 24-hours previously. In the young individual (aged 12-39), SCD can be caused by a range of cardiac conditions, including cardiomyopathy, channelopathies, and coronary artery disease. The risk of SCD varies by condition, as does the diagnostic process and treatment strategies.

The intention of screening for SCD is to detect an underlying cardiac condition, which, through the initiation of early treatment, reduces the likelihood of sudden cardiac death. Potential treatment options include lifestyle changes, drug therapy, and insertion of an implantable cardioverter defibrillator. Standard strategies for screening include a physical assessment and medical history, which may be supplemented by an electrocardiogram (ECG).

The American Heart Association and European Society of Cardiology do not currently support screening the general population for sudden cardiac death, but do support its use in athletes. In relation to athletic screening, there is currently a lack of international consensus regarding the use of the ECG in a screening setting.

Focus of the review

This evidence summary updates the 2014 UK NSC review by assessing relevant evidence published since 2014.

The review sought to answer 3 specific questions, which relate to criteria set out by the UK NSC to determine if a screening programme should be implemented in the UK:

1. What is the reported incidence of sudden cardiac death (SCD) in young individuals aged 12 to 39 years old in the UK? (Question 1 – Criterion 1)
2. In young individuals aged 12 to 39 years old, what is the accuracy of: history-taking; physical examination; 12-lead electrocardiogram (ECG); mobile health devices such as mobile phones, tablets, smart watches and other wearables; and genetic testing as screening tools, alone or in combination, to identify risk of sudden cardiac death? (Question 2 – Criterion 4)
3. What is the effectiveness of screening to prevent sudden cardiac death (SCD) in young individuals aged 12 to 39 years old compared to no screening? (Question 3 – Criteria 11 and 13)

The focus of this review is limited to screening of a general population of asymptomatic young individuals. Screening of symptomatic individuals and athletes is outside the scope of this review. However, where appropriate, the reviewers included evidence from studies of athletes, whilst acknowledging the limitations of using such indirect evidence.

Recommendation under review

The current UK NSC recommendation is that systematic population screening for SCD in the young is not recommended in the UK.

In 2014, the UK NSC review on sudden cardiac death in the young concluded that there were insufficient data to demonstrate that key criteria had been met. In particular, it was reported that there was uncertainty regarding the incidence of SCD and the accuracy of screening tests. The review authors also found no relevant studies that evaluated the effect of screening by comparing outcomes in screened and non-screened individuals.

Findings and gaps in the evidence of this review

The current evidence summary identified 15 studies that met the inclusion criteria for question 1, 18 studies for question 2, and no studies for question 3.

Criterion 1: The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease

marker and serious or treatable disease. **Severity: MET. Incidence: NOT MET. Natural History: NOT CONSIDERED**

The authors of this review assessed the first part of criterion 1 to be met. Sudden cardiac death causes premature death in, seemingly, healthy young individuals, so it is an important health problem based on its severity. There continues to be uncertainty as to the true incidence of SCD, although most studies in the general population reported an incidence of between 1 and 2 cases per 100,000 person-years. Incidence is higher in males and increases with age within the 12-39 age range. Data on the potential impact of athletic status on incidence is inconsistent. Limited data precluded the reviewers from drawing conclusions regarding incidence of sudden cardiac arrest (SCA) or effect of race on incidence.

The authors did not review data related to the second part of criterion 1, namely that the "*natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease*". On this basis, the reviewers are unable to comment on whether this component of the criterion is met.

Criterion 4: There should be a simple, safe, precise and validated screening test. **NOT MET**

This criterion was not met. For the target condition of SCD, data were available from a single study for one testing strategy. Whilst specificity and negative predictive value (NPV) were good, sensitivity and positive predictive value (PPV) were extremely low.

To detect conditions that may lead to SCD as a group, the reviewers examined 7 testing strategies. Due to the failure to follow-up screen-test negative individuals, only PPV could be reported for almost all studies. Across the 44 PPVs calculated, only 3 exceeded 10%. The precision of the estimates for PPV was low. This means that the screening test would cause many individuals to be incorrectly told that they have a heart problem, which may cause anxiety and increase demand on secondary care cardiology services.

Only data from athletic populations were identified for this question, creating concerns regarding the applicability of these data to the general population and highlighting the need for further research.

Criterion 11: There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is

aimed solely at providing information to allow the person being screened to make an "informed choice" (eg. Down's syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened. **NOT MET**
Criterion 13: The benefit gained by individuals from the screening programme should outweigh any harms for example from overdiagnosis, overtreatment, false positives, false reassurance, uncertain findings and complications. **NOT MET**

No studies were found that were relevant to question 3 and met the inclusion criteria. A linked evidence approach is a way of using non-direct evidence to determine whether a criterion has been met. The authors of this review used relevant European Society of Cardiology guidelines to determine if evidence-based strategies exist for treating asymptomatic individuals diagnosed with a condition that may cause SCD. This is important as such treatment strategies are necessary for a screening programme to be effective. Treatment strategies for asymptomatic individuals were identified, but the evidence quality supporting these guideline statements was often low and it was unclear how applicable these guidelines were to a general population. Uncertainties remain as to the impact of overdiagnosis of clinically insignificant disease in the general population, and whether this might lead to overtreatment, such as the unnecessary cessation of sporting activity, which in turn can be detrimental to the overall health of young individuals.

Recommendations on screening

Based on the evidence identified in this review, key criteria for the implementation of a screening programme remain unmet. Therefore, the current evidence does not support a change to the current recommendation against the introduction of a systematic population screening programme for sudden cardiac death in the young in the UK.

Limitations

This review has 3 key limitations. Firstly, in line with UK NSC standard practice, a rapid review methodology was used to review evidence published since 2014. This approach may increase the risk that key publications are missed during the evidence selection process. Secondly, risk of bias in included studies means that there continues to be uncertainty as to the true incidence of SCD and test accuracy of screening tests. In particular, the assessment of question 2 on test accuracy was significantly limited by incomplete follow-up of screen-negative patients in studies. Thirdly, studies often focussed

on athletes, rather than the general population, leading to concerns regarding the applicability and generalisability of the evidence.

Evidence uncertainties

The evidence base in relation to SCD is predominantly based on screening in the young athlete population, rather than the general population. Key areas of uncertainties, some of which were described in the previous 2014 review, were identified in relation to each question. More research is needed to address these uncertainties.

Areas of uncertainty:

Question 1:

- Evidence as to the precise incidence of sudden cardiac death in the UK

Question 2:

- Evidence to determine the test accuracy of screening tests for SCD in the general population

Question 3:

- Development of specific evidence-based guidelines to describe the treatment and lifestyle advice that should be offered to asymptomatic individuals and their families with a diagnosis of a condition that may cause SCD
- Evidence on the potential lifelong impact of screening on individuals and families
- Evidence relating to the effect of offering screening, compared with not offering, on key clinical outcomes, including incidence of SCD and potential harms, such as overtreatment. This evidence should ideally come from a randomised controlled trial. However, before a randomised controlled trial is undertaken, there is need to ensure that screening tests are sufficiently accurate and there are evidence-based guidelines that describe the effective management of asymptomatic individuals with a diagnosed disease

Introduction and approach

Background

The death of a young person is a tragic event, even more so when that death is sudden and unexpected. Cardiac death is one cause of sudden and unexpected death in young people. Sudden cardiac death (SCD) is defined by the American Heart Association as:

> "Sudden and unexpected death occurring within an hour of the onset of symptoms, or occurring in patients found dead within 24 h of being asymptomatic and presumably due to a cardiac arrhythmia or hemodynamic catastrophe."(p e280)(1)

The nature of SCD means that its diagnosis requires an autopsy and may result from the exclusion of other causes. Therefore, the accurate diagnosis of SCD can be challenging.

The screening process for SCD aims to identify the range of cardiovascular conditions that may lead to sudden cardiac death. These conditions typically affect either the heart's structure or the heart's electrical conduction pathways (example conditions shown in table 1). Treatments for these conditions include: ongoing monitoring, lifestyle changes (e.g. avoidance of sport), drug therapy, an implantable cardioverter defibrillator, and surgery.(1, 2) Across these conditions, there are marked differences in prevalence, disease trajectory, treatment options and risk of sudden cardiac death.(3, 4)

The conditions listed in table 1 may lead to the heart suddenly stopping (a cardiac arrest). In the UK, overall survival to hospital discharge following an out-of-hospital cardiac arrest is less than 10%.(5) The mainstay of cardiac arrest treatment is the delivery of chest compressions and defibrillation (electrical shocks to the heart). Short delays in the initiation of these treatments significantly reduce the likelihood of survival.(6-8) In situations where the patient suddenly collapses and treatment is started immediately, high survival rates have been reported.(9, 10) For example, a survival rate of 100% (n=28) was reported in patients with witnessed cardiac arrests at Japanese marathons over 13-year period.(10) In the context of SCD, a key challenge is that around one-third of events happen during sleep, thereby limiting the opportunity for prompt identification and treatment of cardiac arrest.(11-14)

Table 1: Example conditions that may cause sudden cardiac death

Conditions affecting the structure of the heart: Coronary Artery Disease Dilated Cardiomyopathy Hypertrophic cardiomyopathy Marfan Syndrome Arrhythmogenic cardiomyopathy Myocarditis Aortic dissection Conditions affecting the electrical conduction pathway: Brugada syndrome Catecholaminergic Polymorphic Ventricular Tachycardia Short QT syndrome Long QT Syndrome Wolff-Parkinson-White Syndrome (WPW)

Young people with conditions that cause SCD may be asymptomatic or experience only vague and non-specific symptoms.(3) On this basis, the concept of screening for these conditions seems attractive, inasmuch as the early identification of conditions may facilitate early intervention and reduce the associated risk of sudden cardiac death. As such, the key objective of screening is to identify cardiac disease, rather than sudden cardiac death. The screening process typically consists of up to 3 components: medical history, physical examination, and resting ECG. There are a number of potential harms from screening that may impact individuals and their families, such as anxiety or reluctance to engage in sporting activity.

For physical examination and medical history, the American Heart Association has developed a 14-point checklist, which captures elements such as recent symptoms, family history of sudden cardiac death or cardiovascular conditions, blood pressure recordings and detection of heart murmurs.(15) Following recording of an ECG (tracing of the heart's electrical activity), there are a number of criteria that can be used to determine if an individual requires further testing. The most commonly used are the European Society of Cardiology criteria and the Seattle criteria.(16, 17) Importantly, however, these criteria were developed to be applied in the context of pre-participation screening in athletes.

Individuals that are designated as screen-test positive will typically require review by a cardiologist and further investigations to either confirm or rule-out disease. The nature of these tests will depend on the results of the screening test. For example, in a study of UK

footballers, patients with T-wave inversion on the ECG underwent 3 further investigations, namely a cardiac stress test, a cardiac magnetic resonance imaging scan, and 24-hour monitoring of the ECG.(18) In some situations where an abnormality was identified that did not meet disease criteria, annual and biannual follow-up investigations were recommended.

International interest in the screening for SCD in the young was initially driven by the results of an Italian study published in 2006 which examined the impact of the implementation of pre-participation screening programme for athletes aged 12-35 years in the Italian region of Veneto.(19) The study examined the incidence of SCD over a period of 25-years (3 years pre-screening; 22 years post-screening). Compared to the pre-screening period (1979–1981), incidence of SCD in the period 1993–2004 was lower (1979–1981: 4.19 events per 100,000 person-years [95% confidence interval (CI), 1.78–7.59)] v 1993–2004: 0.87 events per 100,000 person-years (95% CI, 0.46–1.28), relative risk 0.21, 95% CI 0.09–0.48). Approximately 2% of athletes screened were excluded from sport. In the non-athlete population that was not subjected to screening, there was no change in incidence of SCD between these periods (risk ratio 1.05, 95% CI 0.69–1.64).

Aside from the before-after study design with its inherent risk of bias, a key concern expressed about the Italian study is the high baseline incidence of SCD (4.19 per 100,000 person-years).(20, 21) The high initial incidence likely results from random annual variation in a condition with a low overall incidence, and therefore the results may simply be driven by bias resulting from regression to the mean. Other commentators have noted the lack of published follow-up data, since the original publication in 2006.(21, 22) The findings from the Italian study have not been replicated elsewhere.(23)

International guidelines do not currently support the screening of the general asymptomatic population. In 2015, the European Society of Cardiology decision to not support population-based screening for SCD was driven by concerns as to limited evidence on test accuracy and the relative advantages and disadvantages of screening.(2) The American Heart Association similarly does not support mass screening.(24)

However, the European Society of Cardiology, Canadian Cardiovascular Society, and American Heart Association do support pre-participation screening in competitive athletes.(2, 24, 25) The European Society of Cardiology based this on a reported increased risk of SCD in this population, and the opportunity to reduce that risk through avoidance of competitive sport.(2) The Society advocates the use of physical examination, medical history and 12-lead ECG as core components of screening in athletes. In contrast, whilst supporting screening, both the American Heart Association and Canadian Cardiovascular Society recommend against the routine use of the 12-lead ECG as a screening tool.(24, 25)

The implementation of these guidelines in practice is variable, both within and between countries.(2, 24-28) For example, a survey of 257 American National Collegiate Athletic Association universities identified that whilst all undertook screening, screening practice met American Heart Association standards in only 8% of universities.(28) In screening programmes that incorporate an ECG, there is variability both in the criteria used to analyse the ECG and the expertise of the clinician that reviews it.(29, 30) These factors may impact the number of individuals classed as screen-test positive and therefore affect test performance and corresponding effectiveness and cost-effectiveness of screening.(30, 31)

A key requirement for any screening programme to be effective is the willingness of the target population to attend screening.(32) For other adult screening programmes in the UK, uptake figures range from 59% (bowel cancer) to 82% (diabetes eye examination).(33) There are relatively few data on SCD screening programme uptake, as most papers describe mandatory programmes, where the individual must be screened to participate in sporting activity. A Spanish screening programme across 4 high schools over 8 years reported a screening uptake of 79%, but uptake varied markedly by year with 92% screened in year 1 and 61% screened in year 6.(34) An American study of 32,561 students at 24 high schools reported an overall uptake rate of 56%, although this varied between 18% and 85% across schools.(35) However, the authors did note that some students may have received a similar examination from their own doctor.

The scope of this review does not cover symptomatic patients and patients with specific clinical characteristics. For individuals that experience a transient loss of consciousness, for example, National Institute of Health and Care Excellence (NICE) guidance recommends assessment with a 12-lead ECG.(36) Similarly, national and international organisations recommend cascade screening in first-degree relatives of individuals that died due to a SCD or who have certain cardiac diagnoses.(1, 2, 37)

Current policy context and previous reviews

The previous UK NSC review on sudden cardiac death in the young was published in 2014.(38) The review, which addressed one main, and 5 subsidiary questions, included 73 studies. The reviewers noted challenges in interpreting data due to the limited volume of peer-reviewed studies. The review concluded that there was uncertainty as to the true incidence of SCD, absence of evidence of diagnostic test accuracy to identify SCD, and absence of evidence of the effectiveness of screening programmes. The evidence examined in the 2014 review informed the current recommendation from the UK NSC that systematic population screening for SCD should not be offered.

In 2015, the Belgian Healthcare Knowledge Centre commissioned a report which examined pre-participation screening in athletes.(3) Parts of the report drew on the UK NSC report.(38) The Belgian report concluded that there was uncertainty as to the clinical benefit of screening for SCD in young athletes, particularly given concerns over the accuracy of screening and the potential for overdiagnosis and overtreatment in cases which would never have become symptomatic.(3)

In line with UK NSC practice for re-appraisal of evidence on screening programmes, this review will provide a timely update on the 2014 review on sudden cardiac death in the young.

Objectives

The objectives of this review are:

- To provide an update on the previous UK NSC review on SCD which reported in 2014,
- To summarise recent literature on the incidence of SCD and SCA (Question 1),
- To summarise recent literature on the accuracy of tests that may be used to screen for SCD or the range of conditions that may cause SCD (Question 2),
- To summarise recent literature on the effectiveness of screening for SCD and estimate the effect of SCD screening on mortality, morbidity, and other key clinical outcomes, including harm associated with overtreatment (Question 3).

Table 2 shows how these objectives link to UK NSC screening criteria, and the number of studies that were included for each question.

Table 2. Key questions for the evidence summary, and relationship to UK NSC screening criteria

	Criterion	Key questions	Studies Included
	THE CONDITION		
1	The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease.	What is the reported incidence of sudden cardiac death (SCD) in young individuals aged 12 to 39 years old in the UK? (Question 1)	15
	THE TEST		
4	There should be a simple, safe, precise and validated screening test.	In young individuals aged 12 to 39 years old, what is the accuracy of: • history-taking; • physical examination; • 12-lead electrocardiogram (ECG); and • mobile health devices such as mobile phones, tablets, smart watches and other wearables • genetic testing	18

	Criterion	Key questions	Studies Included
		as screening tools, alone or in combination, to identify risk of sudden cardiac death? (Question 2)	
	THE SCREENING PROGRAMME		
11	There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (eg. Down's syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.	What is the effectiveness of screening to prevent sudden cardiac death (SCD) in young individuals aged 12 to 39 years old compared to no screening? (Question 3)	0
13	The benefit gained by individuals from the screening programme should outweigh any harms for example from overdiagnosis, overtreatment, false positives, false reassurance, uncertain findings and complications.	As above	As above

Methods

The current review was conducted by the University of Warwick and led by Dr Keith Couper, in keeping with the UK National Screening Committee evidence review process. The review team comprised methodologists, clinical academics, and an information scientist. Database searches were conducted in December 2018 to identify studies relevant to the questions detailed in table 2.

Eligibility for inclusion in the review

On completion of database searches, results were imported into Endnote software and duplicates were removed.

The following review process was then followed:

1. A single reviewer screened each title and abstract against the inclusion/exclusion criteria. Where the applicability of the inclusion criteria was unclear, the article was included at this stage in order to ensure that all potentially relevant studies were captured. A second reviewer provided input in cases of uncertainty, and independently assessed 20% of citations. Any disagreements were resolved by discussion until a consensus was met.
2. Full-text articles required for the full-text review stage were acquired.
3. A single reviewer assessed the eligibility of the full-text paper against the inclusion/exclusion criteria and determined whether the article was relevant to the review question. A second independent reviewer provided input in cases of uncertainty and validated 20% of the first reviewer's screening decisions. Any disagreements were resolved by discussion until a consensus was met.

Eligibility criteria for each question are presented in table 3.

Table 3: Inclusion and exclusion criteria for the key questions

Key question	Inclusion criteria							Exclusion criteria
	Population	**Target condition**	**Intervention**	**Reference Standard**	**Comparator**	**Outcome**	**Study type**	
1	Young individuals aged 12-39	SCD, SCA	-	-	-	Incidence	Cohort studies and systematic reviews of cohort studies	Non-English language; Published prior to 2014 (prior to 2008 for UK studies); Population not comparable to UK (i.e. not European, North American or Australasian study); Published as abstract only
2	Young individuals aged 12-39	SCD; Spectrum of diseases that lead to SCD	Screening by History-taking; Physical examination; Electrocardiogram; Mobile health	Autopsy reports; any recognised reference standard reported in the paper appropriate for	-	Sensitivity; Specificity; Positive predictive value; Negative	Randomised controlled trials, Cross-sectional studies, Cohort	Non-English language; Published prior to 2014;

			devices; Genetic testing (or combination of tests)	specific cardiac defect/abnormality		predictive value	studies, Systematic reviews of any of the above.	Population not comparable to UK (i.e. not European, North American or Australasian study); Published as abstract only
3	Young individuals aged 12 to 39	SCD	Any screening strategy (e.g. population-based screening; pre-participation screening in sports)	-	Usual care	SCD reduction, Overall rates and types of cardiovascular pathology identified, Improvement of any relevant cardiac outcome, Improved quality of life, Overdiagnosis, Overtreatment, Anxiety, Disqualification from sports, Exercise avoidance	Randomised controlled trials, cohort studies, and systematic reviews of any of the above.	Non-English language; Published prior to 2014; Population not comparable to UK (i.e. not European, North American or Australasian study); Published as abstract only

Appraisal for quality/risk of bias tool

The following tools were used to assess the quality and risk of bias of each study included in the review:

- epidemiology studies: JBI Critical Appraisal Checklist for Studies Reporting Prevalence Data(39)
- diagnostic accuracy studies: Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool(40)
- RCTs: Cochrane Collaboration's "Risk of Bias" Tool(41)
- Systematic reviews: Critical Appraisal Skills Programme checklist(42)

Databases/sources searched

An information scientist developed a specific search strategy for each review question. For all questions, Medline and Embase (Ovid platforms) were searched. In addition, the Cochrane library (Wiley interface) for question 3 was searched. Database searches were conducted on 5 December 2018 for question 1 and 2, and on 6 December 2018 for question 3. Search strategies for questions 1, 2 and 3 are included as appendices 1, 4, and 7 respectively.

Question level synthesis

Criterion 1 — Incidence of sudden cardiac death

The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease.

Question 1 – What is the reported incidence of sudden cardiac death (SCD) in young individuals aged 12 to 39 years old in the UK?

The 2014 UK NSC review addressed the question: “how many deaths occur from sudden cardiac deaths in young people?” The review concluded there was uncertainty as to the true incidence of SCD in the young.

Eligibility for inclusion in the review

Cohort studies that described the incidence of SCD and SCA in young individuals aged 12-39 years were included in this review. The key distinction between SCA and SCD is that the incidence of SCA will include individuals who were successfully resuscitated following cardiac arrest.

The age range of interest was pre-defined by UK NSC. The reviewers identified variability in age ranges included across studies and adopted a pragmatic approach to study inclusion. The breakdown of SCD incidence by age reported by Risgaard et al shows that SCD incidence is broadly similar across the early years of life from age one to age 19, followed by a gradual increase to the mid-30s, beyond which point incidence increases markedly.(14) On this basis, studies where the population incorporated persons above 40 years were excluded, except where the study reported a sub-group containing only individuals below 40. Therefore, studies of people above one year of age were included. Studies that included cases below the age of one were excluded due to the risk of conflation between SCD and sudden infant death syndrome. This approach may result in a small under-estimation of the overall incidence and is acknowledged as a limitation.

For the outcome of SCA, the reviewers only included studies where the researchers had sought to exclude cases which were unlikely to be attributable to SCD, for example they excluded cases of cardiac arrest due to trauma and asphyxia.

The main reason for study exclusion at the full-text review stage (n=132) was that the study did not report incidence data in a relevant group. This category was used when the study did not report incidence data (e.g. did not relate number of cases to population at risk), incidence data did not cover the appropriate age category, or the study examined a population that was considered materially different to the UK population.

Seventeen studies were excluded as they only reported cases which occurred in specific locations or at specific times of day, such as at school, during working hours, or whilst playing sport. Seven studies were excluded due to data duplication, that is data from the same dataset were used to answer different research questions across several publications. In the event of identifying studies with overlapping data, the authors of this evidence summary included the study with the longest recruitment period and therefore most cases. The exception to this were 2 Danish studies (Risgaard et al 2014; Winkel et al 2017), where Risgaard et al was included as it provided a detailed and informative breakdown of incidence by age.(12, 14)

Other reasons for exclusion were non-UK studies that were published between 2008 and 2014 (n=16) and ineligible study designs, such as literature reviews (n=4).

The population of interest was that of the general population aged between 12 and 39 years. Additionally, the reviewers planned to stratify data, where possible, by age, ethnicity, sex, and population-type (e.g. general, non-athletes, competitive athletes, non-competitive athletes, elite athletes). These sub-groups are reported where data are available, but sub-groups of sub-groups (e.g. incidence by race in athletic populations) are not considered.

Data were reported as incidence per 100,000 person-years. Incidence was re-calculated where an alternative denominator was used. The reviewers calculated 95% confidence interval data, where it was not reported, and sufficient data were available, using a Poisson distribution in Stata version 15.1 (College Station, Texas, USA). Where necessary, data were extracted from graphs in papers using internet-based software (WebPlotDigitizer version 4.1, Austin, Texas, USA).

Description of the evidence

Database searches yielded 3,943 results, of which 15 were judged to be relevant to this question.(11-14, 18, 23, 43-51) Search strategy is included in Appendix 1.

Appendices 2 and 3 contain a full PRISMA flow diagram (Figure 1, Appendix 2) and a table summarising the characteristics of included publications (Table 15, Appendix 3).

Of the 15 studies included, 13 reported data on the incidence of SCD, one reported incidence of SCA, and one reported incidence of both SCA and SCD. In the 14 studies that reported incidence of SCD, 2 were prospective cohort studies and 12 were retrospective cohort studies. The studies described populations in the UK (n=2), mainland Europe (n=6), USA (n=4), Canada (n=1), and Australasia (n=1).

Study size varied markedly across the included studies. The smallest study reported 8 cases of SCD, whilst the largest study reported 31,492 in a study which used death certificate data from across the USA over a 16-year period.(18, 49)

Discussion of findings

A summary of study quality, based on the Joanna Briggs Institute tool, is included in Appendix 3 (Table 16). The retrospective design of most studies meant the method used to classify SCD events was often sub-optimal, thereby increasing the risk of bias. The process to determine the number of SCD requires 2 stages: firstly, identification of the total number of deaths; and secondly, an assessment of which of these deaths meet the definition of SCD. In some studies, the process used to determine either the total number of deaths or the number of these which met SCD criteria may have led to a significant over-estimation or under-estimation of SCD incidence, particularly given the rarity of SCD. Most studies used government data to determine the number of events, which is likely to be an accurate estimate of the number of deaths. However, 3 studies relied on reporting of deaths by sports teams or identified deaths through internet searches of newspaper articles.(18, 47, 48) This approach will likely under-estimate the incidence of SCD as it is unlikely that all deaths will be identified.

The process of determining whether a death met the definition of SCD was similarly problematic. Most studies used detailed expert review of case history and autopsy reports to classify SCDs, which is likely to be the most effective way to diagnose sudden cardiac death. A key challenge in this approach is that despite most countries requiring autopsies in the event of sudden death, the autopsy rate reported across studies ranged from all cases to less than half of cases.(11, 46) Furthermore, diagnosis of SCD in cases where the cause of death is not structural disease (for example, a channelopathy) may be challenging and is

typically a diagnosis of exclusion, therefore requiring a high-quality autopsy and experienced pathologist. Three studies(44, 46, 49) used ICD-10 codes from death certificates to identify cases of SCD. This approach is likely to over-estimate the number of sudden cardiac deaths as whilst it considers the cause of death, it does not consider the circumstances surrounding the death, which are important in determining whether an event meets the definition of SCD. A previous study demonstrated that this approach significantly over-estimates the true number of sudden cardiac death cases.(52)

Sudden cardiac death

Incidence in the general population was reported in 11 studies (Table 4). Across these studies, reported incidence ranged from 1.01 to 2.89 per 100,000 person-years, with most studies (n=7) reporting an incidence of between one and 2 cases per 100,000 person-years. Of the remaining 4 studies, 2 were Danish studies with some overlap in population. However, the precision of these estimates varied markedly between studies.

A single UK study reported incidence of SCD in the general population.(44) Across the 1–34 years age group, the reported incidence was 1.78 (95% CI, 1.61–1.96) per 100,000 person-years. However, a key limitation to this study is that it determined cases of SCD using death certificate analysis. This approach may lead to an over-estimation of the true incidence as it does not consider the circumstances of the death, which are an essential component of the definition of SCD.

Tables 5 to 8 show incidence across sub-groups of sex (6 studies), race (1 study), sporting activity (5 studies) and age (5 studies). There is consistent evidence from these studies that incidence of SCD is higher in males and increases with age. An American study was the only study to report incidence by race in the general population and reported differences between racial groups with the highest incidence in African-Americans. For many of these studies, 95% confidence intervals were not reported and not estimable from data reported in the paper. Where confidence intervals are reported, precision is often low.

The evidence in relationship to athletic status was less clear as there was not a consistent relationship across studies between incidence and athletic status. Malhotra et al reported SCD incidence in UK adolescent footballers and reported the highest SCD incidence in any of the included studies of 6.8 (95% CI, 2.92–13.32) per 100,000 person-years.(18) However, the low absolute number of SCD events (n=8) means that the precision of this estimate is very low, and differences between studies could be due to design rather than true differences in incidence.

Sudden cardiac arrest

A single included study reported on the incidence of SCA in the general population, with a reported incidence of 2.97 (95% CI, 2.55–3.44) per 100,000 person-years (Table 4).(51) As with SCD, the incidence increased with age, although this was reported in only one study (Table 8).

Harmon et al described incidence of SCA in an athletic population, with a reported incidence of 1.49 per 100,000 person-years (Table 7).(48)

Table 4: Incidence of SCD and SCA by study across general population

Study	Age Range	Incidence per 100,000 person-years	95% Confidence interval
SUDDEN CARDIAC DEATH			
Anastakis 2018	1-35 years	1.8	1.6–2.0
Astrayan 2017	10-39 years	2.89	Not estimable
Bagnall 2016	1-35 years	1.3	1.2–1.4
El-Assad 2017	1-34 years	1.32	Not estimable
Hofer 2014	5-39 years	1.71	1.22–2.33
Maron 2016	14-23 years	2.06	1.36–3.00
Papadakis 2009	1-34 years	1.78	1.61–1.96
Pilmer 2014	15-19 years	1.01	Not estimable
Risgaard 2014	1-35 years	2.3	2.0–2.7
Winkel 2017	1-35 years	2.7	2.5–2.9
Wisten 2017	15-35 years	1.8	1.6–1.9
SUDDEN CARDIAC ARREST			
Allan 2017	18-34 years	2.97	2.55–3.44

Table 5: Incidence of SCD and SCA by sex across general population

Study	Category (sex)	Incidence per 100,000 person-years	95% Confidence interval
SUDDEN CARDIAC DEATH			
Bagnall 2016	Male	1.8	Not estimable
	Female	0.7	Not estimable
El-Assad 2017	Male	1.79	Not estimable
	Female	0.83	Not estimable
Hofer 2014	Male	2.73	Not estimable
	Female	0.69	Not estimable
Pilmer 2014	Male	1.52	Not estimable
	Female	0.47	Not estimable
Risgaard 2014	Male	3.2	2.6–3.8
	Female	1.5	1.1–1.9
Winkel 2017	Male	3.6	3.2–3.9
	Female	1.8	1.5–2.0
SUDDEN CARDIAC ARREST			
No studies			

Table 6: Incidence of SCD and SCA by race across general population

Study	Category (race)	Incidence per 100,000 person-years	95% Confidence interval
SUDDEN CARDIAC DEATH			
El-Assad 2017	White	1.29	Not estimable
	African-American	2.4	Not estimable
	Other	0.85	Not estimable
	Hispanic	0.77	Not estimable
SUDDEN CARDIAC ARREST			
No studies			

Table 7: Incidence of SCD and SCA by sporting activity

Study	Category (athletic status)	Incidence per 100,000 person-years	95% Confidence interval
SUDDEN CARDIAC DEATH			
Astrayan 2017	Non-sport	2.46	Not estimable
	Recreational	0.43	Not estimable
	Competitive	1.19	Not estimable
Harmon 2015	Competitive-Division one	2.28	1.62–3.14
	Competitive-Division two	2.36	1.48–3.58
	Competitive-Division three	1.15	0.69–1.80
Harmon 2016	Competitive	0.99	0.77–1.25
Malhotra 2018	Competitive	6.8	2.92–13.32
Maron 2016	Non-athletes	2.53	1.62–3.77
	Athletes	0.83	0.17–2.42
SUDDEN CARDIAC ARREST			
Harmon 2016	Athletic	1.49	1.22–1.81

Table 8: Incidence of SCD and SCA by age across general population

Study	Category (age in years)	Incidence per 100,000 person-years	95% Confidence interval
SUDDEN CARDIAC DEATH			
Bagnall 2016	11-15	0.4	Not estimable
	16-20	1.32	Not estimable
	21-25	1.11	Not estimable
	26-30	1.91	Not estimable
	31-35	3.2	Not estimable
El-Assad 2017	11-18	0.67	Not estimable
	19-25	1.41	Not estimable
	26-34	2.77	Not estimable
Pilmer 2014	10-14	0.54	Not estimable
	15-19	1.01	Not estimable
Risgaard 2014	12-13	0.9	Not estimable
	14-15	1.2	Not estimable
	16-17	1.7	Not estimable
	18-19	1.0	Not estimable
	20-21	2.7	Not estimable
	22-23	2.7	Not estimable
	24-25	2.8	Not estimable
	26-27	3.4	Not estimable
	28-29	4.0	Not estimable
	30-31	5.2	Not estimable
	32-33	4.2	Not estimable
	34-35	6.9	Not estimable
	36-37	9.1	Not estimable
	38-39	10.9	Not estimable
Winkel 2017	1-18	1.0	0.9–1.2
	19-35	4.4	3.9–4.8
SUDDEN CARDIAC ARREST			
Allan 2017	2-17	0.55	0.34–0.80
	18-34	2.97	2.55–3.44

Summary of Findings Relevant to Criterion 1: Severity: met. Incidence: not met. Natural History: not considered*

The scope of this review was limited to the incidence of SCD and the first component of criterion 1, namely the importance of the health condition judged by its frequency and/or severity.

On the basis of severity, the first part of the criterion was considered met.

There continues to be uncertainty of the incidence of both SCD and SCA in the UK. Across included studies, key methodological weaknesses stemmed from the process used to determine the number and cause of deaths in a population. A single study reported SCD incidence in the UK general population, such that most of the evidence was indirect.

Across studies of SCD, most reported an incidence in the range of 1 to 2 individuals per 100,000 person-years in the general population. Incidence increases with age and is higher in males. Limited data makes it difficult to draw conclusions regarding incidence of SCA and incidence of SCD by race. Data reporting SCD incidence by athletic category were inconsistent.

The authors of this evidence summary did not review data related to the second part of the criterion, namely that the "*natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease.*" On this basis, the reviewers are unable to comment on whether this component of the criterion is met.

* **Met** -for example, this should be applied in circumstances in which there is a sufficient volume of evidence of sufficient quality to judge an outcome or effect which is unlikely to be changed by further research or systematic review.
Not Met - for example, this should be applied in circumstances where there is insufficient evidence to clearly judge an outcome or effect or where there is sufficient evidence of poor performance.
Uncertain -for example, this should be applied in circumstances in which the constraints of an evidence summary prevent a reliable answer to the question. An example of this may be when the need for a systematic review and meta-analysis is identified by the rapid review.

Criterion 4 — Test accuracy

There should be a simple, safe, precise and validated screening test.

Question 2 – In young individuals aged 12 to 39 years old, what is the accuracy of:

- *history-taking;*
- *physical examination;*
- *12-lead electrocardiogram (ECG); and*
- *mobile health devices such as mobile phones, tablets, smart watches and other wearables*
- *genetic testing*

as screening tools, alone or in combination, to identify risk of sudden cardiac death?

The 2014 UK NSC review addressed a similar question, namely: "what screening tests are available and are they reliable?" The discussion noted international variation in the tests used across screening programmes, and a lack of evidence on test accuracy.

Eligibility for inclusion in the review

Cohort studies, randomised controlled trials (RCTs), cross-sectional studies and systematic reviews of these study types were included if they evaluated the test accuracy of one or more key tests in relation to the target conditions of SCD or the group of conditions that may cause SCD in young individuals aged 12 to 39 years.

Pre-defined tests of interest were: history-taking, physical examination, ECG, mobile health devices (e.g. mobile phones, tablets, smart watches and other wearables), genetic testing or a combination of these tests. Test accuracy outcomes were sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). The appropriate reference standard for identifying target conditions was defined as autopsy reports or any recognised reference standard reported in the paper and considered appropriate for the specific cardiac defect/abnormality under consideration.

The main reason for study exclusion at the full-text review stage (n=22) was that the study did not report a relevant population or outcome (n=21). Specifically, 10 studies were excluded due to a non-relevant outcome (for example, studies that described only the frequency of specific ECG abnormalities), 6 studies due to population characteristics (for example, age group of participants or country where study was undertaken), and 5 studies were excluded for multiple reasons (for example, non-relevant population and non-relevant outcome). One study was excluded as it was a literature review (i.e. it was not a systematic

review). Where outcomes were not directly reported, the authors of this review derived outcome from data reported in the paper. Where not reported and sufficient data were available, 95% confidence intervals were calculated using a Poisson distribution in Stata version 15.1 (College Station, Texas, USA).

Description of the evidence

Database searches yielded 3,669 results, of which 17 were judged to be relevant to this question. (Appendix 4) One additional relevant article was identified through the search conducted for question 3, so 18 articles were ultimately included in this review.(18, 31, 53-68) Appendices 5 and 6 contain a full PRISMA flow diagram (Figure 2, Appendix 5) and tables summarising the characteristics of included publications (Tables 21–22, Appendix 6).

Of the 18 included studies, there were 17 cohort studies and one systematic review. Most cohort studies (n=16) included only athletes. Studies were conducted across a range of countries, mainly USA (n=9), UK (n=3), and Australia (n=2). Sample size ranged from 330 to 419,456. Two primary research studies were included in both this analysis and the systematic review, on the basis that the systematic review did not report PPV, so there was no overlap of data.(61, 63, 66)

A single study reported data on test accuracy in relation to SCD, in which the test used was a combination of medical history, physical examination, ECG and echocardiography.

Test accuracy in relation to conditions that may cause SCD was reported in 18 studies (49 outcomes across 7 tests). Table 9 shows the 7 tests where the reviewers were able to extract data across these studies, and the number of studies reporting these tests. Testing using an ECG was broken down according to the criteria used to assess the ECG. None of the included studies reported data on genetic testing or mobile/ electronic health devices. There was variability across studies with regard to who conducted or interpreted these tests.

These tests are routinely performed tests in the clinical setting and are considered safe. Whilst simple to perform, they may require clinical expertise to interpret, particularly in the context of screening for sudden cardiac death.(30)

Table 9: Number of studies reporting each screening test (target conditions: conditions that may cause sudden cardiac death)

Test	Number of studies reporting
Medical history	10
Physical examination	8
ECG- European Society of Cardiology criteria	8
ECG- Seattle criteria	6
ECG- other/ unknown criteria	3
Medical history and physical examination	2
Medical history, physical examination and ECG	12

Discussion of findings

A full assessment of study quality, based on the QUADAS-2 tool is included in Appendix 6 (Tables 23-24).(40) The risk of bias was considered high in the Flow and Timing domain in 15 out of 18 studies. There were also applicability concerns as all studies were considered at high risk of bias in the Patient Selection domain and 15 out of 18 studies in the Index Test domain.

In almost all studies, the population contained only athletes, with the most common age range being teenage years to early 20s. Studies of athletes were eligible, as per our pre-defined eligibility criteria. However, there were concerns regarding the applicability of these data to the asymptomatic general population aged 12-39 in the UK. There are documented differences between the hearts of athletes and non-athletes.(69-71) A screening study reported differences in ECG patterns between athletes and non-athletes, such that a higher proportion of athletes show ECG changes such as T-wave inversion and early repolarisation, whilst a higher proportion of non-athletes have a long corrected QT interval.(72)

The key issue identified across almost all studies was the lack of follow-up in individuals who were categorised as screen-test negative. Instead, an assumption was seemingly made that these individuals did not have a disease that may cause SCD. As such, for these studies, there was no method used to determine if these individuals actually had the target condition, although it is acknowledged that the detailed follow-up of screen-test negative individuals is challenging due to the range of tests required to exclude all conditions that may cause sudden cardiac death. For the majority of studies, this lack of follow-up

precluded calculation of key outcomes, namely sensitivity, specificity, and negative predictive value.

A systematic review, which reported data from 47,137 athletes across 15 studies was included.(63) However, examination of the primary research studies included in the systematic review indicate that these studies were at high risk of bias due to inadequate follow-up of screen-negative individuals. On this basis, data from the systematic review must be interpreted with caution.

Sudden cardiac death

For the outcome of SCD, a single UK-based study of adolescent footballers was included.(18) The screening test comprised a combination of medical history, physical examination, ECG and echocardiography. Screen-test positive individuals were followed-up and treated, where indicated, by a cardiologist. This cohort study included 11,168 individuals, of which 830 (7.4%) were screen-test positive and 10,338 (92.6%) were screen-test negative. Across the cohort, there were 8 (0.07%) SCD during the follow-up period. Of these 8 deaths, 2 (25%) were screen-test positive and 6 (75%) were screen-test negative. As such, the sensitivity was 25% (95% CI 3.2–65.1%), specificity was 92.6% (95% CI 92.1–93.1%), PPV was 0.24% (95% CI 0.0–0.9%), and NPV was 99.9% (95% CI 99.9–100%).

Conditions associated with sudden cardiac death

In studies where the target condition was diseases that may cause SCD, sensitivity and specificity data could only be extracted from 2 studies. In the remaining studies, only PPV could be extracted due to inadequate follow-up of screen-negative individuals. For a number of studies, the PPV was zero, which in part reflects the small sample size and low incidence of the target condition.

Table 10 shows outcome data across all 7 tests. Across studies for each test, there was marked variation in the reported PPV, although the absolute value was consistently low. In only 3 studies did the PPV exceed 10%. The combined test of physical examination, medical history and ECG was reported in 12 studies, of which one study reported a PPV over 10%, and no studies reported a PPV over 20%. Across all studies and tests, one study reported a PPV over 20% which was in relation to ECG analysed using the Seattle criteria. However, this was inconsistent with other studies in the category, which all reported a PPV

of less than 10%. The precision of the estimates for PPV, as shown by the 95% confidence interval, was often very low.

The included systematic review reported sensitivity and specificity data for medical history (sensitivity 20%, specificity 94%), physical examination (sensitivity 9%, specificity 97%), and ECG (sensitivity 94%, specificity 93%), but, as noted above, the limitations in review methodology make these estimates uncertain. For the combined test of physical examination and medical history, Burns et al used a large insurance database (419,456 individuals) to calculate sensitivity (44%) and specificity (96.8%).(58) However, the study methodology relied on a number of assumptions to categorise individuals as being screen-test positive or screen-test negative, leading to a high risk of bias.

Table 10: Outcomes for screening tests (Target condition: conditions that may lead to sudden cardiac death)

Study	Positive predictive value (%) (95% CI)	Other measures
Medical history		
Dhutia 2016	0% (0–5.9)	-
Drezner 2016	0.1% (0.0–0.4)	-
Dunn 2015	0% (0–0.1)	-
Fudge 2014	0.5% (0.1–1.7)	-
Harmon 2015	-	Sensitivity 20% (95% CI, 7–44) Specificity 94% (95% CI, 89–96)
McKinney 2017	4.1% (0.5–14.0)	-
McKinney 2017	0% (0–14.3)	-
Menafoglio 2014	0% (0–23.2)	-
Price 2014	0.4% (0.0–2.3)	-
Snoek 2015	1.3% (0.4–3.3)	-
Physical examination		
Dhutia 2016	0% (0–18.5)	-
Drezner 2016	0.9% (0.0–5.1)	-
Harmon 2015	-	Sensitivity 9% (95% CI, 3–24) Specificity 97% (95% CI, 95–98)
McKinney 2017	0% (0–30.9)	-
Menafoglio 2014	0% (0–21.8)	-
Price 2014	1.3% (0.0–7.0)	-
Snoek 2015	11.1% (0.3–48.3)	-
ECG- European Society of Cardiology criteria		
Brosnan 2014	1.6% (0.3–4.6)	-
Brosnan 2014	0.9% (0.1–3.1)	-
Dhutia 2016	3.0% (1.7–4.9)	-
Dunn 2015	0% (0–0.9)	-
Fudge 2014	6.9% (2.3–15.5)	-
Menafoglio 2014	9.5% (2.7–22.6)	-
Snoek 2015	5.0% (1.9–10.6)	-
Wasfy 2015	0.7% (0.0–3.6)	-
ECG- Seattle criteria		
Brosnan 2014	6.3% (1.3–7.2)	-
Brosnan 2014	2.8% (0.3–9.9)	-
Drezner 2016	6.8% (3.7–11.3)	-
Dunn 2015	0 (0–3.8)	-

Study	Positive predictive value (%) (95% CI)	Other measures
McKinney 2017	28.6% (11.3–52.2)	-
Wasfy 2015	8.3% (0.2–38.5)	-
ECG- Unknown/ other criteria		
Dunn 2015	0% (0–4.6)	-
Harmon 2015	-	Sensitivity 94% (95% CI, 79–98) Specificity 93% (95% CI, 90–96)
Price 2014	8.1% (2.7–17.8)	-
Medical history and physical examination		
Brosnan 2014	0% (0–97.5)	-
Burns 2015	-	Sensitivity 44% Specificity 98.6% (95% CIs not estimable)
Medical history and physical examination and ECG		
Asif 2014	2.7% (1.0–5.7)	-
Asif 2015	3.8% (2.0–6.3)	-
Asif 2017	7.9% (1.7–21.4)	-
Brosnan 2014	1.6% (0.3–4.6)	-
Dhutia 2016	2.6% (1.5–4.2)	-
Fudge 2014	0.9% (0.3–2.2)	-
Ghani 2016	6.5% (0.8–21.4)	-
Malhorta 2018	5.1% (3.7–6.8)	-
McKinney 2017	3.5% (0.4–12.1)	-
McKinney 2017	16.7% (5.6–34.7)	-
Menafoglio 2014	6.0% (1.7–14.6)	-
Snoek 2015	7.3% (3.2–13.8)	-

Summary of Findings Relevant to Criterion 4: Criterion not met†

In view of the evidence identified, the assessment in this evidence summary is limited to the tests of physical examination, ECG, history-taking, and combinations of these tests.

For the outcome of SCD, the single included study reported low sensitivity and extremely low PPV (0.2%), with an estimate that 998 out of every 1000 positive test results would be incorrect.

For the outcome of conditions that may cause SCD, lack of follow-up in screen-test negative individuals in the majority of studies precluded the computation of key outcomes, namely sensitivity, specificity and NPV. The 2 studies that reported sensitivity and specificity were at high risk of bias. Across studies, very low PPVs were observed, which may cause unnecessary anxiety in screen-test positive individuals and their families and would require a large number of individuals to undergo additional testing to confirm or rule out disease. There was variation across studies in the criteria used to determine if an individual was screen-test positive, particularly in relation to ECG analysis. Differences in guidelines between the European Society of Cardiology and American Heart Association as to whether an ECG should form a routine component of screening in athletes highlights a lack of international consensus in screening practice.(2, 24)

Moreover, there were concerns related to the indirectness of the evidence identified. Almost all studies included only individuals that were athletes. In addition, ECG criteria used to determine screening test outcomes were specifically developed for use in athletes.(16, 17) Cardiological differences between athletes and non-athletes limit the generalisability of these data from athletes to a general population.(69-72)

Overall, due to these limitations in the evidence on the accuracy and reliability of the tests under consideration, this criterion is not met.

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† **Met** -for example, this should be applied in circumstances in which there is a sufficient volume of evidence of sufficient quality to judge an outcome or effect which is unlikely to be changed by further research or systematic review.
Not Met - for example, this should be applied in circumstances where there is insufficient evidence to clearly judge an outcome or effect or where there is sufficient evidence of poor performance.
Uncertain -for example, this should be applied in circumstances in which the constraints of an evidence summary prevent a reliable answer to the question. An example of this may be when the need for a systematic review and meta-analysis is identified by the rapid review.

Criteria 11 and 13 — Effectiveness of screening

There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (eg. Down's syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.

The benefit gained by individuals from the screening programme should outweigh any harms for example from overdiagnosis, overtreatment, false positives, false reassurance, uncertain findings and complications.

Question 3 – What is the effectiveness of screening to prevent sudden cardiac death (SCD) in young individuals aged 12 to 39 years old compared to no screening?

The 2014 UK NSC review addressed a similar question and noted that there were no relevant data from randomised controlled trials (RCTs) to answer this question.

Eligibility for inclusion in the review

The reviewers planned to include RCTs, cohort studies, and systematic reviews of cohort studies and RCTs that compared the effect of a screening strategy, compared with usual care, on clinically important outcomes. In line with current UK practice, usual care was defined as no offer or receipt of screening. To be eligible, we required studies to administer intervention and control groups at the same time. Pre-defined outcomes were: incidence of SCD, overall rates and types of cardiovascular pathology identified, change in any relevant cardiac outcome, quality of life, overdiagnosis, overtreatment, anxiety, disqualification from sports, and exercise avoidance.

Studies published prior to 2014, non-English language papers, and studies not undertaken in a population comparable to the UK were excluded.

The main reason for study exclusion at the full-text review stage (n=150) was that the study did not include a comparator group (n=105). Some of these studies had additional reasons for exclusion, such as a non-relevant study population. One study was excluded as it was not published in English (n=1). The remaining papers were non-eligible study types, namely

a commentary or guideline statement (n=37), abstract/ letter/ case report (n=3), or news article (n=3)

Description of the evidence

Database searches (Appendix 7) yielded 2,033 results, of which none were judged to be relevant to this question. Appendix 8 (Figure 3) contains a full PRISMA flow diagram.

Discussion of findings

The search identified no relevant primary research studies.

On this basis, the authors of this evidence summary considered the use of a linked research approach in which non-direct evidence may be used to inform whether the criteria have been met. The following commentary is intended to be a broad overview of some relevant evidence, though it is not based on a systematic review of the literature.

In the context of diagnostic tests, the Australian Medical Services Advisory Committee have devised a linked evidence approach that can be used where there is no direct evidence from RCTs that a diagnostic test improves patient outcome.(73) The approach addresses 4 questions, relating to the safety of the test, the accuracy of the test, the effect of the test outcome on patient management, and the effect of that treatment on health outcomes.

In the context of SCD, the reviewers identified in the preceding section of this report that the test for SCD was safe, but is not accurate. As such, a key component of the linked evidence approach is not met. Nevertheless, the authors considered it helpful to consider the final 2 components, by examining whether the earlier identification of a cardiac condition through screening of an asymptomatic individual would affect clinical management, and thereby impact patient outcome. In the 2015 Belgian review on pre-participation screening, the authors noted that there was uncertainty regarding the benefit of treating asymptomatic individuals in some conditions that may cause sudden cardiac death.(3)

In this section, the European Society of Cardiology guidelines are used to determine the nature of treatment that is recommended in asymptomatic individuals and the evidence strength supporting these recommendations.(2) The European Society of Cardiology guidelines were chosen, in contrast to the ones from the American Heart Association, as these European guidelines are more likely to inform UK cardiology practice. The European

Society of Cardiology categorises recommendations by a numerical category (class I, class II, class IIa, class IIb, class III) and letter (A, B, C). The numerical category describes the type of recommendation ranging from class I, where evidence shows that a treatment or intervention is effective, to class III, where a treatment or intervention is considered ineffective and/or harmful. The letter describes strength of evidence ranging from multiple RCTs or a meta-analysis (A) to expert opinion or retrospective/ registry studies (C).

Hypertrophic cardiomyopathy

European Society of Cardiology guidelines recommend the use of risk stratification in asymptomatic individuals with hypertrophic cardiomyopathy (I-B recommendation). The basis of this risk stratification stems from age, echocardiography parameters, evidence of non-sustained ventricular tachycardia, syncope and family history of sudden death. As such, even asymptomatic individuals, may be deemed to be of sufficient risk of SCD to benefit from an implantable cardioverter defibrillator (IIa-B recommendation). The guidelines also suggest an implantable cardioverter defibrillator may be considered in lower risk patients following a detailed assessment (IIb-B recommendation). Individuals with hypertrophic cardiomyopathy are advised to avoid competitive sporting activity (I-C recommendation).

Dilated cardiomyopathy

Individuals diagnosed with dilated cardiomyopathy are recommended to receive medical therapy to reduce the risks associated the condition (I-A recommendation). Other treatment recommendations are focussed on individuals with ventricular arrhythmias and/ or specific genetic mutations.

Long QT syndrome

In all individuals with long QT syndrome, European Society of Cardiology guidelines recommend the use of beta-blockers, avoidance of QT-prolonging medication, and electrolyte correction as needed (all I-B recommendations). Depending on the individual's genetic mutation or QT interval, other treatments or lifestyle choices may be considered in asymptomatic patients (e.g. avoidance of strenuous swimming or additional drug therapy). The use of an implantable cardioverter defibrillator is recommended only in individuals with previous cardiac arrest (I-B) or syncope/ ventricular tachycardia during beta-blocker treatment (IIa-B).

Comment

Across these 3 conditions, there are treatments that are recommended in asymptomatic individuals. However, the strength of evidence supporting many of these recommendations is categorised as grade B, indicating that is derived from large observational studies or individual randomised trials. This is in line with a recent analysis of European Society of Cardiology and American Heart Association guidelines which identified than fewer than 15% of recommendations across all cardiology guidelines are based on level A (evidence from multiple RCTs) evidence.(74) In the context of European Society of Cardiology sudden cardiac death guidelines, 6.1% recommendations were level A, 38.9% were level B, and 55.1% were level C. This highlights that there is some uncertainty as to the effectiveness of these treatment and lifestyle recommendations.

There is also uncertainty around whether some of the cases of asymptomatic disease detected at screening would actually be overdiagnosis of disease that would not have become symptomatic within the person's lifetime. This would represent harm to those individuals through unnecessary anxiety, medicalisation, avoidance of exercise and other treatments.

Summary of Findings Relevant to Criteria 11 and 13: Criteria not met‡

No studies were identified that directly addressed these criteria.

The use of a linked evidence approach was attempted, but noted that evidence from the previous question did not support the screening test being accurate. The European Society of Cardiology guidelines were reviewed to establish whether treatment options were available for asymptomatic individuals with a diagnosis of a condition that may cause SCD and whether such interventions were effective. Guidelines were identified that support the treatment of asymptomatic individuals with some diseases that may cause SCD. However, these recommendations were rarely underpinned by meta-analyses of

‡ **Met** -for example, this should be applied in circumstances in which there is a sufficient volume of evidence of sufficient quality to judge an outcome or effect which is unlikely to be changed by further research or systematic review.
Not Met - for example, this should be applied in circumstances where there is insufficient evidence to clearly judge an outcome or effect or where there is sufficient evidence of poor performance.
Uncertain -for example, this should be applied in circumstances in which the constraints of an evidence summary prevent a reliable answer to the question. An example of this may be when the need for a systematic review and meta-analysis is identified by the rapid review.

RCTs. Moreover, there may be some uncertainty as to the effectiveness of these interventions, particularly in the general population.

A RCT is required to answer this question, but this review indicates that there is currently a lack of evidence demonstrating good test accuracy and incomplete evidence around treatment efficacy to underpin such a trial.

Review summary

Conclusions and implications for policy

This evidence summary, which updates the review published in 2014, included a total of 33 studies across 3 research questions, thereby informing the UK NSC recommendation regarding the viability, effectiveness and appropriateness of a screening programme for sudden cardiac death in the young.

Sudden cardiac death in the young is an important health problem. Most of the studies identified reported an incidence of SCD in individuals aged 12-39 of between one and 2 cases per 100,000 person-years. However, there remains some uncertainty as to the true incidence of SCD in the general population, particularly in the UK. This review did not attempt to address the second part of criteria 1, namely that "*the natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease*."

Studies of test accuracy in this review typically relied on an assumption that individuals in whom the screening test was negative did not have the disease. This precluded assessment of key outcomes, namely sensitivity, specificity, and negative predictive value. Positive predictive values for tests were typically very low. Across the 44 PPVs calculated, only 3 exceeded 10%. Furthermore, studies were typically undertaken in athletes, thereby limiting their applicability to the general population. No relevant studies were identified that assessed the effectiveness of screening to prevent SCD compared to no screening.

This review did not specifically examine the potential short-term and long-term harms of screening. Low PPVs mean that a high proportion of individuals will be classed as screen-test positive and require follow-up tests. This may lead to anxiety or a reluctance to engage in sporting activity, even after disease has been ruled out. Screening may create increased demand on secondary care services through the need for testing to rule out or confirm disease. There is a need for research to understand the short and long-term harms that may result from screening in the general population.

The findings of this evidence summary are in line with current guideline statements, which do not support screening for SCD in the general population.(1, 2). Other reviews have drawn similar conclusions following a detailed review of the literature.(3) Based on such findings, Denmark has chosen other public health interventions focussed on reducing

mortality in young people (for example, response to cardiac arrest, suicide prevention, and reducing road traffic fatalities) over screening.(75)

Screening for SCD is inevitably complex, given the need to identify a range of cardiac conditions that affect both the structure and electrical pathways in the heart. This is further complicated by a low incidence. Importantly, the assessment that key criteria were not met was primarily driven by a lack of peer-reviewed data that answered the pre-defined research questions with sufficient methodological rigour. The low PPVs reported in test accuracy studies are a significant cause for concern. Furthermore, the low incidence of SCD means that screening tests must have very high specificity to achieve acceptable positive predictive values.

Whilst the volume of peer-reviewed studies on SCD has increased markedly since 2014, many of the key knowledge gaps identified were detailed in the previous UK NSC review.(38) There is a need for additional research:

1. A prospective cohort study to accurately determine the incidence of SCD in the general population of the UK. Such a study should develop a methodology that accurately identifies both the total number of deaths and the number of deaths caused by sudden cardiac death through autopsy across the whole population, similar to that used by Bagnall et al.(11)
2. Cohort studies to identify and test the optimal testing strategy for detecting SCD and conditions that may cause sudden cardiac death. These studies should focus on the general population and ensure adequate follow-up of individuals that are screen-test negative to enable accurate calculation of PPV, NPV, sensitivity, and specificity. The test would require high specificity to achieve acceptable PPV in this low incidence setting.
3. Development of specific evidence-based guidelines to describe the treatment and lifestyle advice that should be offered to asymptomatic individuals with a diagnosis of a condition that may cause sudden cardiac death.
4. Studies on the impact of screening on individuals and families, particularly those with a false positive result and those with a condition where there is no recommended treatment.
5. A RCT to evaluate the effect of offering screening versus not offering screening on key clinical outcomes including incidence of SCD and potential harms, such as overtreatment. There may be challenges in achieving statistical power in such a study due to the small number of cases.

Review findings do not support a change to the current recommendation against the introduction of a systematic population screening programme for sudden cardiac death in the young in the UK.

Limitations

This review is subject to a number of limitations. Firstly, the methodological approach was that of a rapid review, as per the UK NSC standard approach. As such, database searches were limited by year and the reviewers did not undertake some of the strategies recommended by Cochrane to avoid bias and error in the selection of studies, such as the independent review of all titles and abstracts by 2 reviewers.(41) Whilst rapid review methods are accepted for this type of evidence synthesis, some rapid review approaches may produce differing results to systematic reviews.(76-78) In the case of this evidence summary, the consistency of the findings with previous reviews and international guidelines means that it is unlikely that the use of a rapid review methodology impacted on the overall conclusion.

Secondly, there were challenges due to the applicability of evidence. For question 1 (incidence of sudden cardiac death), the age range of 12-39 defined by the UK NSC matched few of the published studies and may not reflect current screening practice. For example, the screening programme delivered by Cardiac Risk in the Young in the UK targets individuals aged between 14 and 35 years.(79) As such, the reviewers carefully considered the inclusion of data from studies that included from a wider range of ages. The decision to include individuals in lower age groups, whilst excluding those in higher age groups was driven by the consistency of incidence data between the target group and individuals with ages outside this group.(14) This strategy may have impacted slightly on the reported incidence. For question 2, the focus of the data on test accuracy in athletes limits the generalisability of the findings to the general population.

Thirdly, the risk of bias in included studies creates uncertainty as to the accuracy of the some of the data reported in this review. The use of validated tools to describe risk of bias enabled the review authors to record these issues. Nevertheless, for question 1, there were issues with the way that sudden cardiac deaths were identified in most studies. In addition, there was often insufficient data presented to enable the calculation of 95% confidence intervals, thereby limiting the precision of point estimates. For question 2, lack of follow-up in screen-test negative individuals precluded key analyses.

Appendix 1 — Search strategy (Question 1)

Electronic databases

The search strategy included searches of the databases shown in Table 11. MEDLINE, MEDLINE In-Process, MEDLINE Epub Ahead of Print and Embase.

Table 11. Summary of electronic database searches and dates

Database	Platform	Searched on date	Date range of search
MEDLINE(R)	Ovid SP	5/12/18	1946 to Present
MEDLINE(R) In-Process & Other Non-Indexed Citations, MEDLINE(R) Epub Ahead of Print	Ovid SP	5/12/18	1946 to Present
Embase	Ovid SP	5/12/18	1980 to Present

Search Terms

Search terms included combinations of free text and subject headings (Medical Subject Headings [MeSH] for MEDLINE, and Emtree terms for Embase), grouped into the following categories:

- disease area: **Sudden cardiac death and cardiac arrest**
- outcome: **Incidence**
- population: **Young population and athletes**
- study design: **Cohort studies and systematic reviews**

Search terms for MEDLINE, MEDLINE In-Process, Epub Ahead of Print and Embase are shown in tables 12 to 14.

Table 12. Search strategy for MEDLINE

Term Group	#	Search terms	Results
Disease area	**1**	Heart Arrest/ep [Epidemiology]	1118
	2	exp Death, Sudden, Cardiac/ep [Epidemiology]	3415
	3	Out-of-Hospital Cardiac Arrest/ep [Epidemiology]	324
	4	(sudden adj3 death).tw,kw.	37052

	5	(Cardiac death or cardiac arrest).tw,kw.	43164
	6	1 or 2 or 3 or 4 or 5	69342
Outcome	**7**	INCIDENCE/	236270
	8	incidence.tw,kw.	598338
	9	7 or 8	696122
	10	6 and 9	8520
Population	**11**	(adolescen* or young* or student* or athlet* or soccer or football*).tw,kw.	948977
	12	exp adolescent/ or exp adult/ or exp Young Adult/ or exp child/	8021644
	13	11 or 12	8293144
	14	10 and 13	5959
Study design	**15**	cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or Retrospective Studies/	1798849
	16	(longitudinal or prospective* or observational or registry).tw,kw.	842718
	17	(autopsy or death certificate*).tw,kw.	64896
	18	(systematic review or meta-analysis).kw,tw.	153355
	19	meta-analysis.pt.	94407
	20	15 or 16 or 17 or 18 or 19	2322437
	21	14 and 20	3764
Limiters	**22**	limit 21 to (english language and humans and yr="2008 - Current")	2205
	23	(letter or comment or editorial or case reports).pt.	3236314
	24	22 not 23	2169

Table 13. Search strategy for MEDLINE(R) In-Process & Other Non-Indexed Citations, MEDLINE(R) Epub Ahead of Print

Term Group	#	Search terms	Results
Disease area	**1**	Heart Arrest/ep [Epidemiology]	0
	2	exp Death, Sudden, Cardiac/ep [Epidemiology]	0
	3	Out-of-Hospital Cardiac Arrest/ep [Epidemiology]	0
	4	(sudden adj3 death).tw,kw.	3863
	5	(Cardiac death or cardiac arrest).tw,kw.	6305
	6	1 or 2 or 3 or 4 or 5	8275
Outcome	**7**	INCIDENCE/	0
	8	incidence.tw,kw.	78344
	9	7 or 8	78344
	10	6 and 9	819
Population	**11**	(adolescen* or young* or student* or athlet* or soccer or football*).tw,kw.	146786
	12	exp adolescent/ or exp adult/ or exp Young Adult/ or exp child/	1
	13	11 or 12	146787
	14	10 and 13	96
Study design	**15**	cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or Retrospective Studies/	0
	16	(longitudinal or prospective* or observational or registry).tw,kw.	134675
	17	(autopsy or death certificate*).tw,kw.	4033

	18	(systematic review or meta-analysis).kw,tw.	4064
	19	meta-analysis.pt.	37
	20	15 or 16 or 17 or 18 or 19	172875
	21	14 and 20	52
Limiters	**22**	limit 21 to english language	52

Table 14. Search strategy for EMBASE

Term Group	#	Search terms	Results
Disease area	**1**	Heart Arrest/ep [Epidemiology]	828
	2	exp Death, Sudden, Cardiac/ep [Epidemiology]	236
	3	Out-of-Hospital Cardiac Arrest/ep [Epidemiology]	200
	4	(sudden adj3 death).tw,kw.	58415
	5	(Cardiac death or cardiac arrest).tw,kw.	82169
	6	1 or 2 or 3 or 4 or 5	115851
Outcome	**7**	INCIDENCE/	332649
	8	incidence.tw,kw.	914238
	9	7 or 8	1021184
	10	6 and 9	14833
Population	**11**	(adolescen* or young* or student* or athlet* or soccer or football*).tw,kw.	1339917
	12	exp adolescent/ or exp adult/ or exp Young Adult/ or exp child/	8876543
	13	11 or 12	9330079
	14	10 and 13	8412
Study design	**15**	cohort studies/ or longitudinal studies/ or	1669883

		follow-up studies/ or prospective studies/ or Retrospective Studies/	
	16	(longitudinal or prospective* or observational or registry).tw,kw.	1438042
	17	(autopsy or death certificate*).tw,kw.	78592
	18	(systematic review or meta-analysis).kw,tw.	249302
	19	15 or 16 or 17 or 18	2853450
	20	14 and 19	3998
Limiters	**21**	21. limit 20 to (human and english language)	3659
	22	22. (letter or editorial).pt.	1593651
	23	23. case report/	2204788
	24	24. 22 or 23	3596628
	25	25. 21 not 24	3559
	26	26. limit 25 to yr="2008 -Current"	2615
	27	27. conference abstract.pt.	3217669
	28	26 not 27	1722

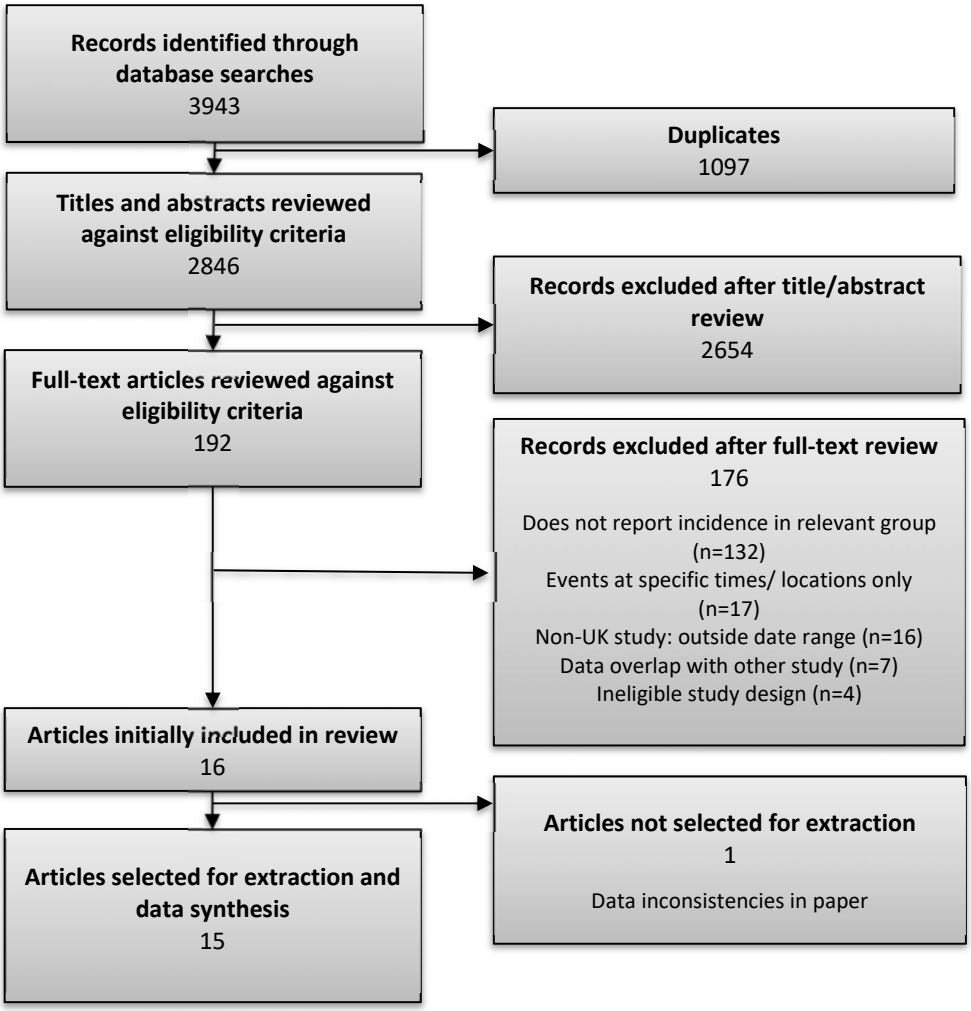
Results were imported into EndNote and de-duplicated.

Appendix 2 — Included and excluded studies (Question 1)

PRISMA flowchart

Figure 1 summarises the volume of publications included and excluded at each stage of the review. Fifteen publications were ultimately judged to be relevant to question 1. Reasons for non-inclusion of studies are summarised in the PRISMA flowchart.

Figure 1: Summary of publications included and excluded at each stage for question 1



Publications included after review of full-text articles

The 15 publications included after review of full-texts are summarised in table 15 (Appendix 3).

Studies were prioritised for extraction and data synthesis. It was planned *a priori* that the following approach would be taken to prioritise studies for extraction:

1. Systematic reviews and meta-analyses would be considered the highest quality of evidence if any were found.
2. Studies would be prioritised if they considered a UK population, followed by studies from Western populations analogous to the UK.

Of the 192 publications included after the review of titles and abstracts, 176 were ultimately judged not to be relevant to this review. One was excluded after an initial decision to include due to concerns regarding data discrepancies within the paper.(80) A list of 192 full-text papers with reasons for inclusion and exclusion is available from the UK NSC.

Appendix 3 — Summary and appraisal of individual studies (Question 1)

Data Extraction

Table 15: Studies relevant to question 1

Study/ Design	Study setting/ recruitment period	Population/ Incidence	Cases/ main causes of death	Identification of deaths/ events	Ascertainment of SCD/ SCA
Allan 2017**(51)** RC	Canada (Toronto) 2009-2012	SCA aged 2-45 General population Incidence: 2.97 per 100,000 person-years	178 SCA 18-34 groups- cause of SCA: 1) Structural myocardial disease 32% 2)Sudden unexplained 28% 3)Coronary heart disease 19%	Cardiac arrest registry	Autopsy/ case data review by authors
Anastasakis 2018**(50)** RC	Greece 2002-2010	SCD aged 1-35 General population Incidence: 1.8 per 100,000 person-years	226 SCD Cause of death: 1) Coronary artery disease 33% 2) SADS 28% 3) Vascular 19%	Government records	Autopsy/ case data review by authors
Asatryan 2017**(23)** RC	Switzerland 1999-2010	SCD aged 10-39 General population Incidence: 2.89 per 100,000 person-years	349 SCD Cause of death: 1) CAD 19% 2) MI 17% 3) HCM 11%	Government records	Autopsy/ case data

Bagnall 2016(11) PC	Australia/ New Zealand 2010-2012	SCD aged 1-35 General population Incidence: 1.3 per 100,000 person-years	490 SCD Cause of death: 1) Unexplained 40% 2) CAD 24% 3) Cardiomyopathies 16%	Government records	Autopsy/ case data review by authors
El-Assad 2017**(49)** RC	USA 1999-2015	SCD aged 1-34 General population Incidence: 1.32 per 100,000 person-years	31492 SCD Cause of death: 1) Arrhythmia 24% 2) Congenital heart disease 21% 3) Ischaemic heart disease 20%	Government records	Death certificate ICD-10 code
Harmon 2016**(48)** RC	USA 2007-2013	SCD/ SCA aged 14-18 Competitive athletes SCD incidence: 0.99 per 100,000 person-years* SCA incidence: 1.49 per 100,000 person-years	69 SCD/ 104 SCA Cause of death: 1) Idiopathic LVH/ cardiomyopathy 26% 2) Unknown 18% 3) Myocarditis 14%	Systematic media searches (Parent Heart Watch database), information from coaches, trainers and parents	Autopsy/ case data review by authors
Harmon 2015**(47)** RC	USA 2003-2013	SCD- students Competitive athletes Incidence: 1.86 per 100,000 person-years†	79 SCD Cause of death: 1) Structurally normal heart 25% 2) Coronary artery anomalies 11% 3= Myocarditis 10% 3= CAD 10%	Systematic media searches (Parent Heart Watch database), National Collegiate Athletic Association Records and insurance claims	Autopsy/ case data review by authors
Hofer 2014**(46)** RC	Swizerland 2000-2007	SCD aged 5-39 General population Incidence: 1.71 per 100,000 person-years	40 SCD Cause of death: 1) MI 30% 2) Cardiac arrest 15% 3= Cardiomyopathy 13%	Government records	Death certificate ICD-10 code

			3= Cardiac arrhythmias 13%		
Malhotra 2018**(18)** PC	1996-2016 UK	SCD- adolescents Competitive athletes Incidence: 6.8 per 100,000 person-years	8 SCD Cause of death: 1) Cardiomyopathy 75% 2= LVH 13% 2= SADS 13%	Voluntary reports, survey of football clubs, internet searches, cardiologist reports	Death certificate/ autopsy data
Maron 2016**(45)** RC	2000-2014 USA	SCD aged 14-23 General population Incidence: 2.06 per 100,000 person-years‡	27 SCD Cause of death: 1= Structurally normal heart 22% 1= HCM 22% 3) CAD 19%	Government records	Autopsy/ case data review
Papadakis 2009**(44)** RC	2002-2005 UK	SCD aged 1-34 General population Incidence: 1.78 per 100,000 person-years	1677 SCD Cause of death 1) Acute MI 25% 2= ARVC 16% 2= Other myocardial disease 16%	Government records	Death certificate ICD-10 code
Pilmer 2014**(43)** RC	2005-2009 Canada	SCD aged 1-19 General population Incidence (15-19 years): 1.01 per 100,000 person-years	44 SCD (15-19 years) Cause of death (all ages) 1) Myocarditis 25% 2= ARVC 16% 2= Other myocardial disease 16%	Government records	Autopsy/ case data review by authors
Risgaard 2014**(14)** RC	2007-2009 Denmark	SCD aged 1-49 General population Incidence (1-35 years): 2.3 per 100,000 person-years	728 SCD (1-35 years) Cause of death: 1) Unexplained 48% 2) CAD 15% 3) ARVC 8%	Government records	Death certificate data (supplemented by information about event and autopsy)

Winkel 2017**(12)** RC	2000-2009 Denmark	SCD aged 1-35 General population Incidence (1-35 years): 2.7 per 100,000 person-years	635 SCD Cause of death: 1) SADS (incl. unexplained)- 45% 2) CAD- 13% 3) Myocarditis-6%	Government records	Death certificate data (supplemented by information about event and autopsy)
Wisten 2017**(13)** RC	2000-2010 Sweden	SCD aged 1-35 General population Incidence (15-35 years): 1.8 per 100,000 person-years	476 SCD (15-35 years) Cause of death: 1) SADS 31%; 2) Coronary artery disease 15%; 3) Myocarditis 14%.	Government records	Autopsy/ case data review by authors

*- calculated from reported figure of 1 per 101,082 person-years/ 1 per 67,064 person-years; †- calculated from reported figure of 1 per 53,703 person-years; ‡- calculated from figure one- total 27 deaths in 1,308,730 person-years

Key: ARVC- Arrhythmogenic right ventricular cardiomyopathy CAD- Coronary artery disease; HCM- Hypertrophic cardiomyopathy; LVH- Left ventricular hypertrophy; MI- Myocardial Infarction; PC- prospective cohort; RC- retrospective cohort; SADS- Sudden Arrhythmic Death Syndrome; SCA- Sudden cardiac arrest; SCD- Sudden cardiac death

Appraisal for quality and risk of bias

Table 16. Quality assessment of studies included in question one

	1-Sample frame appropriate	2-Study participants sampling	3-Sample size adequate	4- Subjects/ setting described	5-Data analysis- coverage of the identified sample	6-Valid methods to identify condition	7-Condition measured in standard, reliable way	8-Appropriate statistical analysis	9-Response rate adequate
Allan (2017)	Unk	Y	Y	Y	Y	N	Y	Y	N/A
Anastasakis (2018)	Unk	Y	Y	Y	Y	N	Y	Y	N/A
Asatryan (2017)	Unk	Y	Y	Y	Y	N	N	N	N/A
Bagnall (2016)	Unk	Y	Y	Y	Y	Y	Y	Y	N/A
El-Assaad (2017)	Unk	Y	Y	Y	Y	N	N	N	N/A
Harmon (2015)	Unk	Y	Y	Y	N	N	N	Y	N/A
Harmon (2016)	Unk	Y	N	N	N	N	N	Y	N/A
Hofer (2014)	Unk	Y	N	N	Y	N	N	Y	N/A
Malhotra (2018)	Unk	Y	N	Y	N	Y	Y	Y	N/A
Maron (2016)	Unk	Y	N	Y	Y	N	Unk	Y	N/A
Papadakis (2009)	Y	Y	Y	N	Y	N	N	Y	N/A
Pilmer (2014)	Unk	Y	N	Y	Y	N	Y	N	N/A
Risgaard (2014)	Unk	Y	Y	Y	Y	N	Unk	Y	N/A
Wisten (2017)	Unk	Y	Y	N	Y	N	Unk	Y	N/A
Winkel (2017)	Unk	Y	Y	Y	Y	N	Unk	Y	N/A

Key: Y- Yes; N- No; Unk- Unknown; N/A- Not applicable
Full list of questions:
1. Was the sample frame appropriate to address the target population?
2.Were study participants sampled in an appropriate way?
3.Was the sample size adequate?
4.Were the study subjects and the setting described in detail?
5.Was the data analysis conducted with sufficient coverage of the identified sample?
6.Were valid methods used for the identification of the condition?
7.Was the condition measured in a standard, reliable way for all participants?
8.Was there appropriate statistical analysis?
9.Was the response rate adequate, and if not, was the low response rate managed appropriately?

Appendix 4 — Search strategy (Question 2)

Electronic databases

The search strategy included searches of the databases shown in table 17. MEDLINE, MEDLINE In-Process, MEDLINE Epub Ahead of Print and Embase.

Table 17. Summary of electronic database searches and dates

Database	Platform	Searched on date	Date range of search
MEDLINE(R)	Ovid SP	5/12/18	1946 to Present
MEDLINE(R) In-Process & Other Non-Indexed Citations, MEDLINE(R) Epub Ahead of Print	Ovid SP	5/12/18	1946 to Present
Embase	Ovid SP	5/12/18	1980 to Present

Search Terms

Search terms included combinations of free text and subject headings (Medical Subject Headings [MeSH] for MEDLINE, and Emtree terms for Embase), grouped into the following categories:

- disease area: **Sudden cardiac death and conditions that cause sudden cardiac death**
- population: **Young population and athletes**
- outcome: **Sensitivity, specificity and associated concepts**
- test interventions: **Physical examination, medical history and other pre-defined tests.**

Search terms for MEDLINE, MEDLINE In-Process, Epub Ahead of Print and Embase are shown in tables 18 to 20.

Table 18. Search strategy for MEDLINE

Term Group	#	Search terms	Results
Disease area	**1**	heart arrest/ or death, sudden, cardiac/ or out-of-hospital cardiac arrest/	7914
	2	exp brugada syndrome/ or exp long qt syndrome/ or exp	3049

		ventricular fibrillation/ or exp ventricular flutter/	
	3	arrhythmias, cardiac/ or Tachycardia, Ventricular/ or Wolff-Parkinson-White Syndrome/	6891
	4	exp Heart Diseases/di, pc [Diagnosis, Prevention & Control]	40611
	5	exp Cardiac Conduction System Disease/	8130
	6	exp Cardiomyopathies/	12149
	7	(channelopath* or long QT syndrome or catecholaminergic polymorphic ventricular tachycardia or brugada or Wolff-Parkinson-White).tw,kw.	2004
	8	(cardiomyopath* or arrhythmogenic right ventricular cardiomyopathy).tw,kw.	10504
	9	((Sudden adj2 death) or (cardiac arrest or cardiac death)).tw,kw.	12106
	10	((cardiac or cardiovascular) adj2 (disorder* or condition*)).tw,kw.	2830
	11	exp Myocardial Infarction/	18111
	12	exp Coronary Disease/	21613
	13	(coronary adj2 artery).tw,kw.	22031
	14	myocardial infarction.tw,tw.	21705
	15	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	103702
Population	**16**	(adolescen* or young* or student* or athlet* or soccer or football*).tw,kw.	176412

	17	exp adolescent/ or exp adult/ or exp Young Adult/ or exp child/	1141191
	18	16 or 17	1186936
	19	15 and 18	62778
Outcome	**20**	exp "Sensitivity and Specificity"/	109264
	21	(specificity or sensitivity or accuracy).tw,kw.	189011
	22	((false adj2 positive) or (false adj2 negative) or (true adj2 negative) or (true adj2 positive)).tw,kw.	8444
	23	diagnostic odds ratio.tw,kw.	682
	24	exp Diagnostic Errors/	14902
	25	20 or 21 or 22 or 23 or 24	265720
	26	19 and 25	10560
Test interventions	**27**	exp Medical History Taking/	1842
	28	((history adj2 taking) or family history).tw.	8661
	29	Physical Examination/	4365
	30	physical exam*.tw,kw.	9064
	31	exp Electrocardiography/	16845
	32	(electrogardiogram or ECG).tw,kw.	7353
	33	"Monitoring, Ambulatory"/	1725
	34	((wearable or ambulatory) adj2 (device* or monitor*)).tw,kw.	1320
	35	(genetic adj2 (test* or screen*)).tw,kw.	6978
	36	Genetic Testing/	6508
	37	27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36	52917
	38	26 and 37	2315

Limiters	**39**	limit 38 to (english language and humans)	2252
	40	(letter or comment or editorial or case reports).pt.	446948
	41	39 not 40	1993
	42	limit 41 to yr="2014-current"	1993

Table 19. Search strategy for MEDLINE(R) In-Process & Other Non-Indexed Citations, MEDLINE(R) Epub Ahead of Print

Term Group	#	Search terms	Results
Disease area	**1**	heart arrest/ or death, sudden, cardiac/ or out-of-hospital cardiac arrest/	0
	2	exp brugada syndrome/ or exp long qt syndrome/ or exp ventricular fibrillation/ or exp ventricular flutter/	0
	3	arrhythmias, cardiac/ or Tachycardia, Ventricular/ or Wolff-Parkinson-White Syndrome/	0
	4	exp Heart Diseases/di, pc [Diagnosis, Prevention & Control]	0
	5	exp Cardiac Conduction System Disease/	0
	6	exp Cardiomyopathies/	0
	7	(channelopath* or long QT syndrome or catecholaminergic polymorphic ventricular tachycardia or brugada or Wolff-Parkinson-White).tw,kw.	1552
	8	(cardiomyopath* or arrhythmogenic right	7249

		ventricular cardiomyopathy).tw,kw.	
	9	((Sudden adj2 death) or (cardiac arrest or cardiac death)).tw,kw.	8221
	10	((cardiac or cardiovascular) adj2 (disorder* or condition*)).tw,kw.	2084
	11	exp Myocardial Infarction/	0
	12	exp Coronary Disease/	0
	13	(coronary adj2 artery).tw,kw.	15785
	14	myocardial infarction.tw,tw.	14552
	15	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	42194
Population	**16**	(adolescen* or young* or student* or athlet* or soccer or football*).tw,kw.	146874
	17	exp adolescent/ or exp adult/ or exp Young Adult/ or exp child/	1
	18	16 or 17	146875
	19	15 and 18	2677
Outcome	**20**	exp "Sensitivity and Specificity"/	0
	21	(specificity or sensitivity or accuracy).tw,kw.	166659
	22	((false adj2 positive) or (false adj2 negative) or (true adj2 negative) or (true adj2 positive)).tw,kw.	5538
	23	diagnostic odds ratio.tw,kw.	338
	24	exp Diagnostic Errors/	0
	25	20 or 21 or 22 or 23 or 24	169868
	26	19 and 25	115
Test interventions	**27**	exp Medical History Taking/	0

	28	((history adj2 taking) or family history).tw.	7232
	29	Physical Examination/	0
	30	physical exam*.tw,kw.	8080
	31	exp Electrocardiography/	0
	32	(electrogardiogram or ECG).tw,kw.	5017
	33	"Monitoring, Ambulatory"/	0
	34	((wearable or ambulatory) adj2 (device* or monitor*)).tw,kw.	1438
	35	(genetic adj2 (test* or screen*)).tw,kw.	5450
	36	Genetic Testing/	0
	37	27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36	25941
	38	26 and 37	36
Limiters	**39**	limit 38 to (english language and humans)	36
	40	limit 39 to yr="2014-current"	28

Table 20. Search strategy for EMBASE

Term Group	#	Search terms	Results
Disease area	**1**	heart arrest/ or death, sudden, cardiac/ or out-of-hospital cardiac arrest/	65256
	2	exp brugada syndrome/ or exp long qt syndrome/ or exp ventricular fibrillation/ or exp ventricular flutter/	40863
	3	arrhythmias, cardiac/ or Tachycardia, Ventricular/ or Wolff-Parkinson-White Syndrome/	39448

	4	exp Heart Diseases/di, pc [Diagnosis, Prevention & Control]	246973
	5	exp Cardiac Conduction System Disease/	83248
	6	exp Cardiomyopathies/	120377
	7	(channelopath* or long QT syndrome or catecholaminergic polymorphic ventricular tachycardia or brugada or Wolff-Parkinson-White).tw,kw.	18404
	8	(cardiomyopath* or arrhythmogenic right ventricular cardiomyopathy).tw,kw.	101676
	9	((Sudden adj2 death) or (cardiac arrest or cardiac death)).tw,kw.	115068
	10	((cardiac or cardiovascular) adj2 (disorder* or condition*)).tw,kw.	22481
	11	exp Myocardial Infarction/	329912
	12	exp Coronary Disease/	285695
	13	(coronary adj2 artery).tw,kw.	245701
	14	myocardial infarction.tw,tw.	229053
	15	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	1061778
Population	**16**	(adolescen* or young* or student* or athlet* or soccer or football*).tw,kw.	1339917
	17	exp adolescent/ or exp adult/ or exp Young Adult/ or exp child/	8876543
	18	16 or 17	9330079
	19	15 and 18	521597
Outcome	**20**	exp "Sensitivity and Specificity"/	310757

	21	(specificity or sensitivity or accuracy).tw,kw.	1466669
	22	((false adj2 positive) or (false adj2 negative) or (true adj2 negative) or (true adj2 positive)).tw,kw.	81533
	23	diagnostic odds ratio.tw,kw.	2058
	24	exp diagnostic error/pc [Prevention]	577
	25	20 or 21 or 22 or 23 or 24	1623867
	26	19 and 25	33243
Test interventions	**27**	family history/	95279
	28	((history adj taking) or family history).tw,kw.	98831
	29	Physical Examination/	190265
	30	physical exam*.tw,kw.	101380
	31	exp Electrocardiography/	126914
	32	(electrogardiogram or ECG).tw,kw.	93999
	33	"Monitoring, Ambulatory"/	10572
	34	((wearable or ambulatory) adj2 (device* or monitor*)).tw,kw.	11735
	35	(genetic adj (test* or screen*)).tw,kw.	46722
	36	Genetic Testing/	41499
	37	27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36	613896
	38	26 and 37	7186
Limiters	**39**	limit 38 to (human and english language and yr="2014 -Current")	2452
	40	case report/	2204788
	41	(letter or editorial).pt.	1593651
	42	40 or 41	3596628
	43	39 not 42	2241

44	conference abstract.pt.	3217669
45	43 not 44	1648

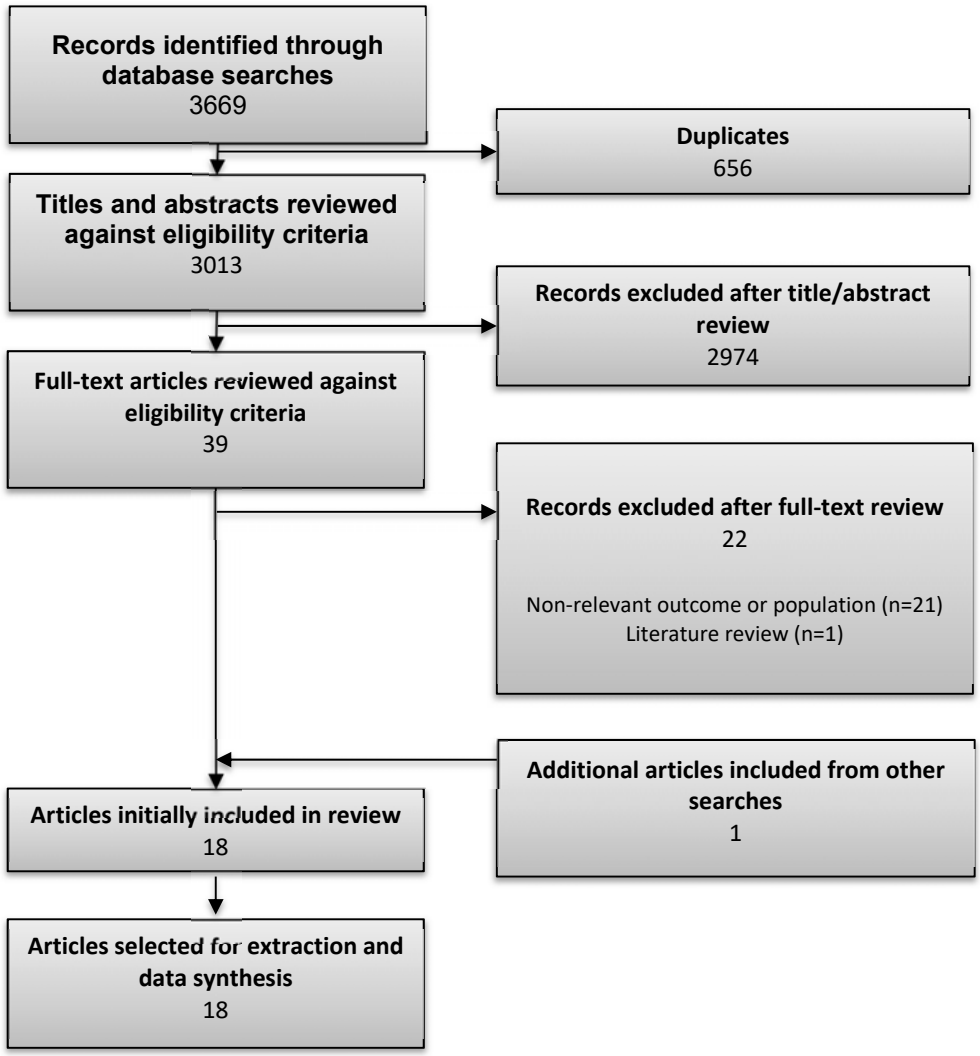
Results were imported into EndNote and de-duplicated.

Appendix 5 — Included and excluded studies (Question 2)

PRISMA fowchart

Figure 2 summarises the volume of publications included and excluded at each stage of the review. Eighteen publications were ultimately judged to be relevant to question 2. Reasons for non-inclusion of studies are summarised in the PRISMA flowchart.

Figure 2: Summary of publications included and excluded at each stage for question 2



Publications included after review of full-text articles

The 18 publications included after review of full-texts are summarised in tables 21-22 (Appendix 6).

Studies were prioritised for extraction and data synthesis. It was planned *a priori* that the following approach would be taken to prioritise studies for extraction:

1. Systematic reviews and meta-analyses would be considered the highest quality of evidence if any were found.
2. Studies would be prioritised if they considered a UK population, followed by studies from Western populations analogous to the UK.

Of the 39 publications included after the review of titles and abstracts, 22 were ultimately judged not to be relevant to this review. A list of the 39 full-text papers with reasons for inclusion and exclusion is available from the UK NSC.

Appendix 6 — Summary and appraisal of individual studies (Question 2)

Data Extraction

Table 21: Studies relevant to question 2 (target condition: sudden cardiac death)

Study/ Design	Study setting/ recruitment period	Population	Test/ % screen-test positive	Screening programme	Outcome
Malhotra 2018**(18)** Prospective cohort	UK 1996-2016	11,168 Adolescent footballers Mean age 16.4 years 95% male	Medical history, physical examination, ECG, echocardiography (7.43%)	One-off Results reviewed by expert cardiologist	Sensitivity 25% (95% CI 3.2 to 65.1%) Specificity 92.6% (95% CI 92.1 to 93.1%) PPV 0.24% (95% CI 0.0 to 0.9%) True +ve 2/830 False +ve 828/830 NPV 99.9% (95% CI 99.9 to 100%) True –ve 6/10338 False –ve 10332/10338

Table 22: Studies relevant to question 2 (target condition: conditions that may cause sudden cardiac death)

Study/ Design	Study setting/ recruitment period	Population	Test/ % screen-test positive	Screening programme frequency/ who delivered	Outcome
Asif 2014**(53)** Prospective cohort	USA	802 High school athletes Mean age 15.5 years 51% male 71.2% Caucasian/ 10.6% Asian	American Heart Association history questionnaire (Medical history), physical examination and ECG (Seattle criteria) (28.18%)	One-off Unknown	PPV 2.65% True +ve- 6/226 False +ve 220/226
Asif 2015**(54)** Prospective cohort	USA	1516 athletes Mean age 15.6 years 59.3% male 56.2% Caucasian/ 24.5% African-american or black	American Heart Association history questionnaire (Medical history), physical examination and ECG (Seattle criteria) (22.82%)	One-off Unknown	PPV 3.76% True +ve 13/346 False +ve 333/346
Asif 2017**(55)** Prospective cohort	USA	1192 athletes Median age 19 years 55.4% male 80.4% white/ 7.2% black	Medical history, physical examination and ECG (Seattle criteria) (3.19%)	One-off Unknown	PPV 7.89% True +ve- 3/38 False +ve 35/38
Brosnan 2014**(56)** Prospective cohort	Australia 2011-2012	1078 Elite athletes Mean age 20 years 82% male 86% White/ 7% Indigenous Australian	Medical history and physical examination (0.09%)	One-off Usually by cardiologist. All reviewed by cardiologist.	PPV 0% True +ve- 0/1 False +ve 1/1
			ECG (ESC criteria) (17.25%)	One-off Usually by cardiologist. All reviewed by cardiologist.	PPV 1.61% True +ve 3/186 False +ve 183/186
			ECG (Seattle criteria) (4.45%)	One-off Usually by cardiologist. All reviewed by cardiologist.	PPV 6.25% True +ve 3/48 False +ve 45/48
				One-off	PPV 1.60%

			Combination (History, Physical and ECG) (17.35%)	Usually by cardiologist. All reviewed by cardiologist.	True +ve 3/187 False +ve 184/187
Brosnan 2014**(57)** Prospective cohort	Australia 2011-2013	1261 Elite athletes Mean age 20.6 years 78.9% male 86% White/ 12% Indigenous Australian	ECG (ESC criteria) (18.08%)	One-off Screening by 2 experienced cardiologists	PPV 0.88% True +ve- 2/228 False +ve 226/228
			ECG (Seattle criteria) (5.63%)	One-off Screening by 2 experienced cardiologists	PPV 2.82% True +ve 2/71 False +ve 69/71
Burns 2015**(58)** Retrospective cohort	USA 2005-2009	419,456 athletes (examination for sports competition) Mean age 14 years	History/ physical examination (1.71%)	One-off Unknown	Sensitivity 44% Specificity 96.8%
Dhutia 2016(31) Prospective cohort	UK 2011-2014	4925 athletes Mean age 19.9 years 83% male 85% White/ 9% Afro-Caribbean	History (1.24%)	One-off Screening by experienced sports cardiologist	PPV 0% True +ve 0/61 False +ve 61/61
			Physical examination (0.37%)	One-off Screening by experienced sports cardiologist	PPV 0% True +ve 0/18 False +ve 18/18
			ECG (modified ESC criteria) (10.19%)	One-off Screening by experienced sports cardiologist	PPV 2.99% True +ve 15/502 False +ve 487/502
			Combination (History, Physical and ECG) (11.80%)	One-off Screening by experienced sports cardiologist	PPV 2.58% True +ve 15/581 False +ve 566/581
Drezner 2016**(59)** Prospective cohort	USA 2012-2014	5258 athletes Mean age 20.1 years 55% male 73% Caucasian/ 16% African-American	American Heart Association history questionnaire (Medical history) (33.28%)	One-off Unknown	PPV 0.1% True +ve 2/1750 False +ve 1748/1750
			Physical examination (2.05%)	One-off Unknown	PPV 0.9% True +ve 1/108

					False +ve 107/108
			ECG (Seattle criteria) (3.65%)	One-off Interpreted by cardiologist	PPV 6.8% True +ve 13/192 False +ve 179/192
Dunn 2015**(60)** Prospective cohort	USA	1596 athletes Mean age 19.7 years 62% male 65% White/ 19% African-American	American Heart Association history questionnaire (Medical history) (23.81%)	One-off Administered by medical staff or volunteers (follow-up by sports medicine physician if positive reply)	PPV 0% True +ve 0/380 False +ve 380/380
			ECG (ESC criteria) (26.82%)	One-off ECGs reviewed for accuracy by an expert in sports cardiology	PPV 0% True +ve 0/428 False +ve 428/428
			ECG (Seattle criteria) (5.95%)	One-off ECGs reviewed for accuracy by an expert in sports cardiology	PPV 0% True +ve 0/95 False +ve 95/95
			ECG (Stanford criteria) (4.89%)	One-off ECGs reviewed for accuracy by an expert in sports cardiology	PPV 0% True +ve 0/78 False +ve 78/78
Fudge 2014**(61)** Prospective cohort	USA 2010-2011	1339 Mixed population (80% in organised sports team) Age 63% aged 16-20 49% male 68% Caucassian/ 18% Asian or Pacific islander	Medical history- self-report questionnaire (31.44%)	One-off Physician interview including review of questionnaire	PPV 0.48% True +ve 2/421 False +ve 419/421
			Physical examination (9.26%)	One-off Blood pressure by firefighters. Physician examination/ interview	Data not reported
			ECG (ESC criteria) (5.38%)	One-off	PPV 6.94% True +ve 5/72

				Interpreted by experienced sports medicine or cardiology physician	False +ve 67/72
			Combined (History, Physical and ECG) (40.03%)	One-off As individual components above	PPV 0.93% True +ve 5/536 False +ve 531/536
Ghani 2016**(62)** Prospective cohort	England 2010-2012	1191 Elite rughby players Mean age 22.5 years 100% male 85.6% Caucassian/ 5.5% Afro-Carribbean	Medical history, physical examination, ECG, echocardiography (2.85%)	One-off Screening manager, cardiac physiologist, cardiology fellow	PPV 6.45% True +ve 2/31 False +ve 29/31
Harmon 2015**(63)** Systematic review and meta-analysis	European countries, USA, Algeria, Dubai, Qatar 19972-2014	47,137 individuals across 15 studies 13 of 15 studies included only athletes Age range 5-39 66% male	Medical history	Varied across studies	Sensitivity 20% Specificity 94%
			Physical examination	Varied across studies	Sensitivity 9% Specificity 97%
			12-lead ECG	Varied across studies	Sensitivity 94% Specificity 93%
Malhotra 2018**(18)** Prospective cohort	UK 1996-2016	11,168 Adolescent footballers Mean age 16.4 years 95% male	Medical history, physical examination, ECG, echocardiography (7.43%)	One-off Results reviewed by expert cardiologist	PPV 5.06% True +ve 42/830 False +ve 788/830
McKinney 2017**(64)** Prospective cohort	Canada 2013-2015	PHASE1 680 competitive athletes Mean age 19.6 years 73.7% male 76.2% Caucasian/ 8.2% Asian	Modified American Heart Association history questionnaire (Medical history) (7.21%)	One-off Physician present	PPV 4.1% True +ve 2/49 False +ve 47/49
			Physical examination (1.47%)	One-off Cardiologists, cardiology fellows, internal medicine residents	PPV 0% True +ve 0/10 False +ve 10/10
				One off	PPV 3.51%

			Combination (History, Physical and ECG) (8.38%)	As individual components above. ECG interpretation by cardiologist	True +ve 2/57 False +ve 55/57
		PHASE 2 679 competitive athletes Mean age 20.7 years 56.8% male 72.6% Caucasian/ 11.0% Asian	Medical history questionnaire (developed by authors) (3.53%)	One-off Non-physicians	PPV 0% True +ve 0/24 False +ve 24/24
			Combined (History, ECG) (4.42%)	One-off As history above. ECG interpretation by cardiologist	PPV 16.67% True +ve 5/30 False +ve 25/30
		PHASE 1 and 2 Mean age 1359 years 65.3% male 74.4% Caucasian/ 9.6% Asian	ECG (Seattle criteria) (1.55%)	One-off ECG interpretation by Cardiologist	PPV 28.6% True +ve 6/21 False +ve 15/21
Menafoglio 2014**(65)** Prospective cohort	Switzerland 2011-2012	1070 competitive athletes Mean age 19.7 years 75.2% male 97.9% Caucassian	Medical history (1.31%)	One-off Cardiologist/ sports physician	PPV 0% True +ve 0/14 False +ve 14/14
			Physical examination (1.40%)	One-off Cardiologist/ sports physician	PPV 0% True +ve 0/15 False +ve 15/15
			ECG (ESC criteria) (3.93%)	One-off Cardiologist/ sports physician	PPV 9.52% True +ve 4/42 False +ve 38/42
			Combination (History, Physical and ECG) (6.26%)	One-off As individual components above	PPV 5.97% True +ve 4/67 False +ve 63/67
Price 2014**(66)**	USA 2010-2011	2017 High School athletes Age range 14-18 years 71% male	Medical history based on AHA questionnaire (12.10%)	One-off Nurse	PPV 0.41% True +ve 1/244 False +ve 243/244

Prospective cohort		34% Caucassian/ 31% Black or African-American	Physical examination (3.82%)	One-off Unknown	PPV 1.30% True +ve 1/77 False +ve 76/77
			ECG (3.07%)	One-off Cardiac technician	PPV 8.06% True +ve 5/62 False +ve 57/62
Snoek 2015**(67)** Retrospective cohort	Holland 2011	561 athletes/ military Median age 18 years 71% male	Medical history (55.26%)	One-off Sports physician/ sports physician trainee/ physician assistant	PPV 1.29% True +ve 4/310 False +ve 306/310
			Physical examination (1.60%)	One-off Sports physician/ sports physician trainee/ physician assistant	PPV 11.11% True +ve 1/9 False +ve 8/9
			ECG (ESC criteria) (21.39%)	One-off Member of sports medicine and cardiology department	PPV 5.00% True +ve 6/120 False +ve 114/120
			Combination (History, Physical and ECG) (19.61%)	One-off As individual components above	PPV 7.27% True +ve 8/110 False +ve 102/110
Wasfy 2015**(68)** Prospective Cohort	USA 2006-2013	330 college rowers Mean age 18.9 years 56% male 91% Caucasian/ 3% Afro-Caribbean	ECG (ESC criteria) (46.67%)	One-off Cardiologist	PPV 0.65% True +ve 1/154 False +ve 153/154
			ECG (Seattle criteria) (3.63%)	One-off Cardiologist	PPV 8.3% True +ve 1/12 False +ve 11/12

Appraisal for quality and risk of bias

Quality assessments of included studies are reported below.

Table 23: Quality assessment of studies included in question 2 (target condition: sudden cardiac death)

	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Malhotra (2018)	Low	Low	Low	Low	High	Low	Low

Table 24: Quality assessment of studies included in question 2 (target condition: conditions that may cause sudden cardiac death)

	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Asif (2014)	Low	Unk	Unk	High	High	High	Unk
Asif (2015)	Low	Low	Unk	High	High	High	Low
Asif (2017)	Low	Unk	Unk	High	High	Unk	Unk
Brosnan (2014)	Low	Low	Low	High	High	High	High
Brosnan (2014)	Low	Low	Unk	High	High	High	Unk
Burns (2015)	High	High	High	High	High	High	High
Dhutia (2016)	Low	Low	Low	High	High	High	Low
Dreznor (2016)	Low	Low	Low	Unk	High	High	Low
Dunn (2015)	Unk	Low	Low	High	High	High	Low
Fudge (2014)	Low	Low	High	High	High	Low	Low
Ghani (2016)	Unk	Low	Low	High	High	High	Low
Harmon (2015)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Malhotra (2018)	Low	Low	Low	High	High	High	Low
McKinney (2017)	Low	Low	Low	High	High	High	Low
Menafoglio (2014)	Low	Low	Low	High	High	High	Low
Price (2014)	Low	Low	Low	Low	High	High	Low
Snoek (2015)	Low	Low	Low	High	High	High	Low
Wasfy (2015)	Low	Low	Low	High	High	High	Low

Key: Unk- Unknown; N/A- Not applicable

Appendix 7 — Search strategy (Question 3)

Electronic databases

The search strategy included searches of the databases shown in table 25. MEDLINE, MEDLINE In-Process, MEDLINE Epub Ahead of Print, Embase and the Cochrane Library.

Table 25. Summary of electronic database searches and dates

Database	Platform	Searched on date	Date range of search
MEDLINE(R)	Ovid SP	6/12/18	1946 to Present
MEDLINE(R) In-Process & Other Non-Indexed Citations, MEDLINE(R) Epub Ahead of Print	Ovid SP	6/12/18	1946 to Present
Embase	Ovid SP	6/12/18	1980 to Present
Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials	Wiley Online	6/12/18	Issue 12 of 12, December 2018

Search terms included combinations of free text and subject headings (Medical Subject Headings [MeSH] for MEDLINE, and Emtree terms for Embase), grouped into the following categories:

- disease area: **Sudden cardiac death**
- population: **Young population and athletes**
- intervention: **Screening**
- study design: **Randomised controlled trials, cohort studies and systematic reviews**

Search terms for MEDLINE, MEDLINE In-Process, Epub Ahead of Print, Embase, and Cochrane Library are shown in tables 26 to 29.

Table 26. Search strategy for MEDLINE

Term Group	#	Search terms	Results
Disease area	**1**	heart arrest/ or death, sudden, cardiac/ or out-of-hospital cardiac arrest/	7914
	2	((Sudden adj2 death) or (cardiac arrest or cardiac death)).tw,kw.	12106
	3	1 or 2	14297

Population	**4**	(adolescen* or young* or student* or athlet* or soccer or football*).tw,kw.	176412
	5	exp adolescent/ or exp adult/ or exp Young Adult/ or exp child/	1141191
	6	4 or 5	1186936
Intervention	**7**	Mass Screening/	12147
	8	screen*.tw,kw.	121178
	9	7 or 8	123570
Study design	**10**	(randomized controlled trial or controlled clinical trial).pt.	87688
	11	meta-analysis.pt.	39519
	12	exp cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/	384772
	13	(random* or blind* or trial or cohort or longitudinal or prospective* or observational or registry or systematic review or meta-analysis).tw,kw.	493142
	14	10 or 11 or 12 or 13	699524
	15	3 and 6 and 9 and 14	233
	16	3 and 9	672
	17	2 and 14	5730
	18	3 and 6	8800
	19	3 and 6 and 9	534
Limiters	**20**	limit 19 to (english language and humans)	500
	21	(letter or editorial or comment or case reports).pt.	446948
	22	20 not 21	429
	23	limit 22 to yr="2014 - Current"	429

Table 27. Search strategy for MEDLINE(R) In-Process & Other Non-Indexed Citations, MEDLINE(R) Epub Ahead of Print

Term Group	#	Search terms	Results
Disease area	**1**	heart arrest/ or death, sudden, cardiac/ or out-of-hospital cardiac arrest/	0
	2	((Sudden adj2 death) or (cardiac arrest or cardiac death)).tw,kw.	8221
	3	1 or 2	8221
Population	**4**	(adolescen* or young* or student* or athlet* or soccer or football*).tw,kw.	146874
	5	exp adolescent/ or exp adult/ or exp Young Adult/ or exp child/	1
	6	4 or 5	146875
Intervention	**7**	Mass Screening/	0
	8	screen*.tw,kw.	89637
	9	7 or 8	89637
Study design	**10**	(randomized controlled trial or controlled clinical trial).pt.	298
	11	meta-analysis.pt.	37
	12	exp cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/	0
	13	(random* or blind* or trial or cohort or longitudinal or prospective* or observational or registry or systematic review or meta-analysis).tw,kw.	362146
	14	10 or 11 or 12 or 13	362170
	15	3 and 6 and 9 and 14	24
	16	3 and 9	357

	17	2 and 14	2222
	18	3 and 6	893
	19	3 and 6 and 9	118
Limiters	**20**	limit 19 to (english language and humans)	114
	21	limit 20 to yr="2014 - Current"	78

Table 28. Search strategy for EMBASE

Term Group	#	Search terms	Results
Disease area	**1**	heart arrest/ or death, sudden, cardiac/ or out-of-hospital cardiac arrest/	65256
	2	((Sudden adj2 death) or (cardiac arrest or cardiac death)).tw,kw.	115068
	3	1 or 2	141108
Intervention	**4**	exp screening/	603927
	5	screen*.tw,kw.	908660
	6	4 or 5	1137299
Limiters	**7**	(letter or editorial).pt.	1593651
	8	case report/	2204788
	9	conference abstract.pt.	3217669
	10	7 or 8 or 9	6682238
	11	3 and 6	6981
	12	11 not 10	3854
	13	limit 12 to (human and english language and yr="2014 -Current")	1313

Table 29. Search strategy for the Cochrane Library Databases (Searched via the Wiley Online platform)

Term Group	#	Search terms	Results
	1	((sudden near/2 death) OR “cardiac death” OR “cardiac	213

	arrest) AND screen* in Title Abstract Keyword

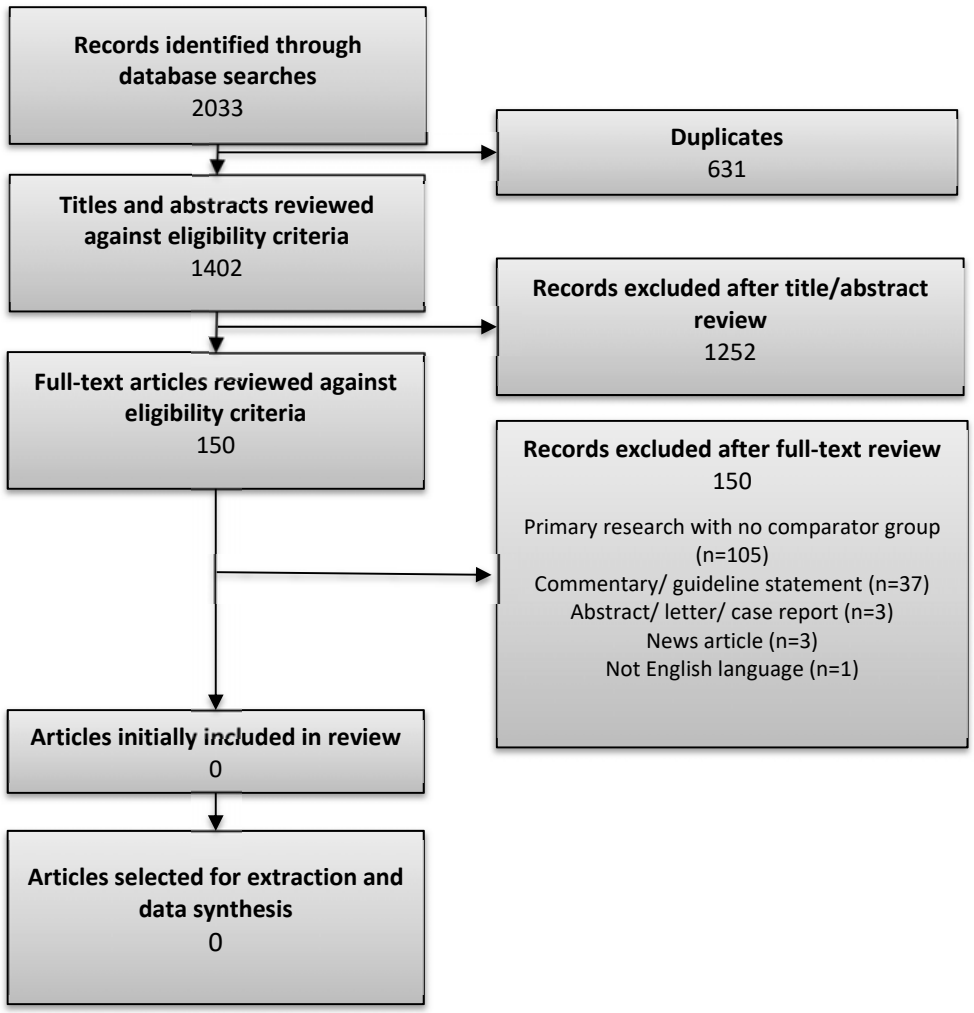
Results were imported into EndNote and de-duplicated.

Appendix 8 — Included and excluded studies (Question 3)

PRISMA flowchart

Figure 3 summarises the volume of publications included and excluded at each stage of the review. No publications were found that were relevant to question 3. Reasons for non-inclusion of studies are summarised in the PRISMA flowchart.

Figure 3: Summary of publications included and excluded at each stage for question 3



Publications included after review of full-text articles

No publications were included after review of full-texts.

Studies were prioritised for extraction and data synthesis. It was planned *a priori* that the following approach would be taken to prioritise studies for extraction:

1. Systematic reviews and meta-analyses would be considered the highest quality of evidence if any were found.
2. Studies would be prioritised if they considered a UK population, followed by studies from Western populations analogous to the UK.

Of the 150 publications included after the review of titles and abstracts, 150 were ultimately judged not to be relevant to this review. A list of the 150 full-text papers with reasons for exclusion is available from the UK NSC.

Appendix 9 – UK NSC reporting checklist for evidence summaries

All items on the UK NSC Reporting Checklist for Evidence Summaries have been addressed in this report. A summary of the checklist, along with the page or pages where each item can be found in this report, is presented in table 30.

Table 30. UK NSC reporting checklist for evidence summaries

	Section	Item	Page no.
1.	TITLE AND SUMMARIES		
1.1	Title sheet	Identify the review as a UK NSC evidence summary.	Title page
1.2	Plain English summary	Plain English description of the executive summary.	5-6
1.3	Executive summary	Structured overview of the whole report. To include: the purpose/aim of the review; background; previous recommendations; findings and gaps in the evidence; recommendations on the screening that can or cannot be made on the basis of the review.	7-11
2.	INTRODUCTION AND APPROACH		
2.1	Background and objectives	Background – Current policy context and rationale for the current review – for example, reference to details of previous reviews, basis for current recommendation, recommendations made, gaps identified, drivers for new reviews Objectives – What are the questions the current evidence summary intends to answer? – statement of the key questions for the current evidence summary, criteria they address, and number of studies included per question, description of the overall results of the literature search.	12-19

		Method – briefly outline the rapid review methods used.	
2.2	Eligibility for inclusion in the review	State all criteria for inclusion and exclusion of studies to the review clearly (PICO, dates, language, study type, publication type, publication status etc.) To be decided *a priori*.	20-21
2.3	Appraisal for quality/risk of bias tool	Details of tool/checklist used to assess quality, e.g. QUADAS 2, CASP, SIGN, AMSTAR.	22
3.	SEARCH STRATEGY AND STUDY SELECTION (FOR EACH KEY QUESTION)		
3.1	Databases/ sources searched	Give details of all databases searched (including platform/interface and coverage dates) and date of final search.	22
3.2	Search strategy and results	Present the full search strategy for at least one database (usually a version of Medline), including limits and search filters if used. Provide details of the total number of (results from each database searched), number of duplicates removed, and the final number of unique records to consider for inclusion.	48-53, 60-69, 79-84
3.3	Study selection	State the process for selecting studies – inclusion and exclusion criteria, number of studies screened by title/abstract and full text, number of reviewers, any cross checking carried out.	19
4.	STUDY LEVEL REPORTING OF RESULTS (FOR EACH KEY QUESTION)		
4.1	Study level reporting, results and risk of bias assessment	For each study, produce a table that includes the full citation and a summary of the data relevant to the question (for example, study size, PICO, follow-up period, outcomes reported, statistical analyses etc.). Provide a simple summary of key measures, effect estimates and confidence intervals for each study where available. For each study, present the results of any assessment of quality/risk of bias.	Study level reporting: 55-58, 71-77 Quality assessment: 59,78

4.2	Additional analyses	Describe additional analyses (for example, sensitivity, specificity, PPV, etc.) carried out by the reviewer.	55-58, 71-77
5.	QUESTION LEVEL SYNTHESIS		
5.1	Description of the evidence	For each question, give numbers of studies screened, assessed for eligibility, and included in the review, with summary reasons for exclusion.	24-25, 33-34, 41
5.2	Combining and presenting the findings	Provide a balanced discussion of the body of evidence which avoids over reliance on one study or set of studies. Consideration of four components should inform the reviewer's judgement on whether the criterion is 'met', 'not met' or 'uncertain': quantity; quality; applicability and consistency.	25-30, 34-38, 41-43
5.3	Summary of findings	Provide a description of the evidence reviewed and included for each question, with reference to their eligibility for inclusion. Summarise the main findings including the quality/risk of bias issues for each question. Have the criteria addressed been 'met', 'not met' or 'uncertain'?	31, 39, 43-44
6.	REVIEW SUMMARY		
6.1	Conclusions and implications for policy	Do findings indicate whether screening should be recommended? Is further work warranted? Are there gaps in the evidence highlighted by the review?	45-47
6.2	Limitations	Discuss limitations of the available evidence and of the review methodology if relevant.	47

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