UK National Screening Committee

Screening for familial hypercholesterolaemia in children

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

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Plain English summary

Familial hypercholesterolaemia (FH) is an inherited condition that causes a person to have very high cholesterol (fat) in the blood. It is caused by a faulty gene that stops the body from getting rid of low density lipoprotein (LDL) 'bad' cholesterol. This 'bad' cholesterol then builds up in the blood vessels putting the person at risk of developing heart disease in their early adult life. The cholesterol build-up usually starts from childhood.

This review aimed to see if there is evidence to support the introduction of a screening programme for FH in children in the UK. A screening programme would likely involve a blood test to see whether a child has high cholesterol. If they did, they could then have a blood test to see if they had inherited one of the faulty FH genes. The aim would be to diagnose FH at a young age so that the child could start treatment to stop them getting heart disease when they get older. Treatment usually involves a healthy diet combined with medication to reduce cholesterol. The usual medications are called statins. It is recommended that children with FH start statins from 10 years of age.

The review found that:

1. A big study has tested whether a child screening programme might be possible. The study tested the cholesterol of around 10,000 children aged 1–2 years. Cholesterol was tested by a simple heel prick. The study found that about half of the children with a faulty FH gene did not have high cholesterol. But almost one third of children with high cholesterol did not have a faulty FH gene. So, it is still not clear which is the best screening test to use to find out who will benefit from a treatment.
2. There was no evidence to tell us whether screening children for FH would reduce their risk of developing heart disease. There is evidence to show that statin treatment in children reduces their cholesterol level, but this has only looked at the effect for a short period (one year). So, we need more information on the effect of statins on longer periods.
3. There was no evidence to tell us whether screening children for FH could cause any harm or side effects. There is evidence to show that statin treatment in children is safe for up to 2 years, but studies need to show they are safe for use in the long-term. We also need to know that screening would not cause any extra problems like causing excessive worry among children or parents or affect the child's quality of life.

These uncertainties suggest that further research is needed. There is currently not enough evidence to recommend a child screening programme for FH in the UK.

Executive summary

Purpose of the review

This evidence summary aims to evaluate whether the evidence available supports the introduction of a population screening programme for familial hypercholesterolaemia (FH) in children.

Background

FH is a common hereditary cause of very high blood cholesterol, estimated to affect between 1 in 250 and 1 in 500 of the white European population.[1-3] The liver of affected individuals has reduced capacity to clear low-density lipoprotein cholesterol (LDL-C) from the blood, leading to the early development of atherosclerosis and premature coronary heart disease.[1, 2, 4] The vast majority of cases are caused by disease-causing variants (mutations) of the gene that codes for the LDL receptor (*LDLR*), with apolipoprotein B (*APOB*) and proprotein convertase subtilisin/kexin Type 9 (*PCSK9*) gene variants accounting for a small number of others.[1, 3]

FH has an autosomal dominant pattern of inheritance. This means that if a parent carries an FH-causing gene variant (mutation) they have a 1 in 2 chance of passing this variant onto their child. This is known as heterozygous FH (HeFH). Children with HeFH usually have LDL-C elevation about 2-3 times the norm, above 4.0 or 5.0mmol/L.[3] They are likely to be asymptomatic and the condition may not be detected clinically until the development of cardiovascular symptoms at a later age. Very rarely a child can inherit an FH gene variant from both parents resulting in the rare and severe condition of homozygous FH (HoFH). The LDL-C level in these children is usually elevated above 11mmol/L and without early treatment they will develop cardiovascular disease in childhood or adolescence.[3, 5]

Universal screening for FH is not currently performed in the UK. The National Institute for Health and Care Excellence (NICE) recommends a cascade testing system.[6] When an index case (usually an adult) is diagnosed with FH, cascade testing involves offering DNA testing to their first-, second- and sometimes third-degree relatives. This would therefore include any children. Children diagnosed with HeFH are recommended to start lipid-lowering therapy (usually a statin) from the age of 10 years. Children with HoFH require much more intensive therapy with LDL apheresis, which removes LDL from the blood. This would usually be started by 8 years of age and sometimes much younger.[5]

Focus of the review

The current review aimed to assess whether the evidence is available to support the introduction of a universal child screening programme for FH. Such a screening programme would most likely involve cholesterol testing in all children at a particular age. If their cholesterol was above a certain level this would likely be followed by DNA testing to see if they carried an FH-associated gene variant. The purpose would be to support early diagnosis so that children with FH could start lifestyle management and lipid-lowering therapy early, and so reduce their risk of premature cardiovascular disease.

This review update addressed 3 key questions:

1. What are the optimum age and test cut-off values (total cholesterol [TC] and/or LDL-C concentration [mmol/l]) for screening children for FH? – addressing Criterion 5 (there should be a simple, safe and precise screening test)
2. Does universal screening for FH in children reduce FH-related morbidity and mortality in the screened individual? – addressing Criterion 11 (there should be evidence from high quality randomised controlled trials that the programme is effective in reducing morbidity and mortality)
3. Are there harms from universally screening children for FH? – addressing Criterion 13 (the benefit gained by individuals from the screening programme should outweigh any harms)

A rapid review search for these questions was conducted in January 2019 for studies published from 2015 onwards for the first 2 questions, both of which were addressed by the last 2016 evidence review, as below. Question 3 on harms was not specifically addressed by the last evidence review and so the literature search for this question was extended back to 2008.

Recommendation under review

The UK National Screening Committee (NSC) does not currently recommend universal child screening for FH. This policy was informed by the last external evidence review on this topic, which was published in 2016.[7]

The last review did not identify any studies that had examined the performance of universal child screening in practice. The review found one 2007 systematic review[8] of case-control studies which aimed to determine the age and the cholesterol cut-offs that best discriminated between children with and without FH. This review identified 1–9 years as the optimal age group for screening, with some studies suggesting that peak performance would be achieved at age 1–2 years. Consequently, a UK pilot study was commenced to evaluate the performance of universal screening children at the time of routine immunisation at age 1–2 years; results of this pilot were not yet available at the time.

The 2016 review did not find any studies evaluating whether universal child screening reduces morbidity or mortality from FH. Very little evidence was available on the ethical issues and acceptability of universal screening in children, including the management of screen-detected children.

The review aimed to see whether new evidence is available that has assessed universal child FH screening in practice, looked at the effects on morbidity and mortality, and assessed whether there may be any harm from screening. Due to the paucity of evidence on the last point around the ethics of screening, this review update aimed to widen this question to encompass any perceived or actual harms from universal screening.

Findings and gaps in the evidence of this review

Overall this evidence summery found that there is still uncerainty around a potential screening programme for familial hypercholesterolaemia in children in the UK.

Optimum age, test and cut-off values to use in an FH screening programme
This update review identified two UK cohort studies that assessed the test performance of the TC and/or LDL-C cut-off values identified by the 2007 systematic review[8] to give the best discrimination between children with and without FH. One was the large prospective pilot study[9] in progress at the time of the last evidence review, which assessed the TC cut-off (1.53 multiples of the median [MoM]) in 10,000 children aged 1–2 years. The second was a smaller retrospective study[10] that evaluated the same TC cut-off, in addition to the LDL-C cut-off (1.84 MoM), using blood samples collected from children aged 9 years.

Both studies found that this TC cut-off had poor sensitivity for identifying children with FH as defined by carriage of an FH gene variant. Around half of children with FH variants had a TC below the cut-off. Meanwhile almost a third of children detected in the prospective study did not have FH gene variants and were diagnosed on the basis of having 2 sequential cholesterol samples above the threshold (multifactorial/polygenic FH). There is some remaining uncertainty over the natural history of this condition and whether it is distinct from FH, as such this could represent a high rate of over-diagnosis in a screening programme. The prospective study[9] proposed lowering the TC cut-off to 1.35 MoM, which would detect more children with an FH variant, and defining FH as either TC above this lower threshold plus an FH variant or 2 repeat raised cholesterols aged at age 1–2 years. However, this has to be tested in practice.

Another option may be to raise the screening age and/or use LDL-C as the test rather than TC. The retrospective cohort[10] found some evidence that screening using LDL-C at 9 years of age may give a better indication of whether FH variants are going to raise

cholesterol/cardiovascular risk. This could also have the benefit of positioning screening and diagnosis at the time when treatment (lipid-lowering therapy) could start. However, as this was a retrospective analysis based on few cases, more evidence is needed to confirm this as the appropriate age for a screeing programme and LDL-C as the preferable test.

Therefore questions remain about the optimal age to screen and the test (TC and/or LDL-C) and cut-offs to use. There also appears to be a need for consensus on how FH should be definitively diagnosed in the context of a universal screening programme, whether by the carriage of gene variants and/or positive family history indiciative of FH, or by raised cholesterol alone, given this is the mediator of cardiovascular risk.

Benefits and harms of universal FH screening in children

This update review identified no evidence assessing whether universal screening affects FH-related morbidity or mortality compared with no screening. Neither did it identify any studies that have performed follow-up of universal screening programmes to see whether any aspect of the screening, diagnosis and management process may be associated with any adverse effects.

The review therefore assessed the benefits and harms of statins or other lipid-lowering therapy, given that this is the management approach that would be used for children detected through a universal screening programme.

Currently, children in the UK are diagnosed with FH on the basis of cholesterol level, clinical signs and/or family history, or an identified gene variant alone (usually in the context of cascade testing). Diagnosed children are managed under the care of a specialist according to the National Institute for Health and Care Excelence (NICE) guildence, which recommends that children with heterozygous FH start a statin by age 10 years (children with rare HoFH need treatment at a younger age). The treatment recommendations of the NICE guideline were informed by a 2014 Cochrane review, the 2016 update of which[11] was identified by this evidence review.

The Cochrane review[11] summarised moderate quality evidence that statin treatment in children or adolescents diagnosed with FH reduces LDL-C and TC in the short to medium term up to one year. It found limited, low quality evidence that statins may reduce intermediate markers of atherosclerosis at up to 2 years. No information was available on the effect of statins on cholesterol levels or cardiovascular outcomes in the longer term.

Looking at potential harms, the Cochrane review[11] found moderate to low quality evidence that statins in children or adolescents with FH are not associated with increased risk of adverse effects, liver toxicity, myopathy or effects on onset of puberty in the short to

medium term at up to 1–2 years. This is supported by data in the UK Paediatric FH Registry.[12] No data is available on longer term safety, or on outcomes including quality of life, neurological or cognitive effects, glycaemic control, hormonal effects and later fertility.

A universal screening programme would identify children with FH who may otherwise have been detected clinically or via the cascade testing system, and who would fall under the remit of the NICE treatment recommendations informed by this Cochrane review. For these children meeting diagnostic criteria for FH, the benefits from starting statins are considered to outweigh any potential harms, even given the lack of direct evidence on longer term outcomes.

However, there is no current recommendation on the management of children with multifactorial/polygenic FH who could be identified through a population screening programme. For children with high cholesterol alone, there is no evidence available to inform the risk-benefit balance from starting lifelong statin therapy in childhood.

Overall the volume, quality, applicability and direction of the evidence examined do not comprehensively answer the key questions.On this basis none of the criteria examined in this review update were addressed satisfactorily.

Recommendations on screening

The findings indicate that the current policy not to perform universal screening for FH in children should not be reversed at the current time.

Limitations

The search strategy was built on a protocol developed *a priori* for each of the 3 key questions. Searching was limited to 3 literature databases and did not include grey literature resources. Studies only available in non-English language, editorials, abstracts, conference reports or poster presentations were not included. The reviewers were also unable to contact study authors or review non-published material. Background information on the ethics issues and potential controversy around universal screening was not based on a systematic search for evidence on this topic, and as such relevant literature or views may have been omitted.

Evidence uncertainties

Further study may help to address the remaining uncertainties identified by this evidence review update:

1. Consensus on the diagnostic criteria that should be used to definitively diagnose FH in children identified through universal screening would be valuable. It may be helpful to better understand the genotype-phenotype relationship to see whether certain FH gene variants carry higher risk of a child developing phenotypic FH and early atherosclerosis. Similarly, further study may help to understand whether the polygenic/multifactorial condition carries the same risk as monogenic FH or whether it should be considered a distinct condition. Understanding these aspects of the natural history of FH may help to inform the appropriate screening test when considering that a number of young children who carry FH variants may have lower cholesterol, while others may have raised cholesterol despite having no identified gene variant.
2. Long-term RCTs assessing whether universal screening (or treatment) of children with FH affects long-term cardiovascular morbidity and mortality may be neither ethical nor feasible. However, comparative studies would be useful to understand whether screening (or treatment) improves intermediate markers of atherosclerosis in the medium term, such as carotid intima-media thickness or endothelial function. It would also be beneficial to see whether this could differ by diagnostic criteria used for FH, age at treatment initiation, the statin or dose given.
3. Follow-up of universally screened populations would be helpful to see that the full screening programme is not associated with any harm, such as from over-diagnosis (e.g. children diagnosed with multifactorial/polygenic FH on the basis of elevated cholesterol alone, without confirmation through compatible family history/clinical signs), misclassification or missed diagnoses (e.g. those with monogenic FH who do not have raised cholesterol in young childhood) or psychological or quality of life effects.
4. Similarly, further follow-up of treated children with FH would be beneficial to see whether statins or other management approaches are safe in the longer term and do not have adverse effects on quality of life, liver and muscle function, neurological and cognitive development, diabetes, or growth and reproduction. Again, it would helpful to see whether this may differ by diagnostic criteria used for FH, age at treatment, statin or dose given.
5. Future studies are needed to directly assess the views of the UK public and healthcare professionals towards universal screening for FH in young children; for example, whether there are any reservations towards early and lifelong treatment.

Introduction and approach

Background

Familial hypercholesterolemia (FH) is a common hereditary cause of very high blood cholesterol. The liver of affected individuals has reduced capacity to clear low-density lipoprotein cholesterol (LDL-C) from the blood due to a lack of functioning LDL receptors. The subsequent deposition of excess LDL-C in the arteries is believed to be in progress from birth leading to the early development of atherosclerosis.[3] FH is the most common hereditary cause of premature coronary heart disease among the general European population.[2, 4]

Most cases of FH are caused by disease-causing variants (mutations) of the gene coding for the LDL receptor (*LDLR*). Over 1,700 disease-causing variants of this gene have been identified.[1, 3] Variants of the genes coding for apolipoprotein B (*APOB*) which binds to the LDLR, and proprotein convertase subtilisin/kexin Type 9 (*PCSK9*) which is involved in the degradation of the LDLR, are believed to account for, respectively, around 5% and 1% of cases.[1, 3] However, for up to a third of people displaying the FH phenotype (raised cholesterol), a mutation in one of these genes will not be identified.[3] These cases are often termed polygenic and may result from disease variants in unidentified genes, or possibly they could be multifactorial involving lifestyle factors, rather than classic monogenic, dominantly inherited FH.

The autosomal dominant pattern of FH inheritance means that if a person inherits a single copy of a disease-causing variant from one of their parents they will develop phenotypic FH. This is known as heterozygous FH (HeFH). A person with HeFH has a 1 in 2 chance that they will pass the condition onto their child. The prevalence of HeFH among the white European population was thought to be 1 in 500,[2] but recent estimates suggest it may be as high as 1 in 200 or 1 in 250.[1, 3] If 2 parents with HeFH have a child there is a 1 in 4 chance that the child will inherit 2 disease-causing variants, one from each parent. This results in the rare and severe condition of homozygous FH (HoFH), believed to affect around 1 in a million people of the European population.[5] Children with HoFH typically show clinical signs of lipid deposition (tendon or cutaneous xanthomata) and have excessively high LDL-C (above 11mmol/L) before the age of 10 years.[5] If the condition remains untreated, such individuals will develop cardiovascular disease in childhood or adolescence.[3] By comparison, children with HeFH would typically have LDL-C elevated above 4.0 or 5.0mmol/L[3] and would not normally show disease manifestations in childhood. Unless their cholesterol is tested, the condition is unlikely to be clinically detected until cardiovascular symptoms develop at some time in adulthood.

Current diagnosis and management in the UK

Population-wide (universal) child screening for FH is not current performed in the UK. Children with FH are currently detected either as a result of clinically-indicated cholesterol testing or via the current UK system of cascade testing.

The National Institute for Health and Care Excellence (NICE) recommend that FH is suspected in adults with a total cholesterol (TC) above 7.5mmol/l and/or a family history of premature heart disease (before age 60) in a first-degree relative.[6] Diagnosis in adults is made using either the Simon Broome or Dutch Lipid Clinical Network (DLCN) criteria, which are based on a combination of family history, clinical signs, LDL-C concentration and/or DNA testing. When an index case is diagnosed, cascade testing involves offering DNA testing to their first-, second- and sometimes third-degree relatives. Cascade testing would therefore include any children of a parent with FH. It is recommended that children are tested at the earliest opportunity, ideally before the age of 10 years.[6]

NICE specify that all people with an identified FH variant 'have an unequivocal diagnosis of FH even if their LDL-C concentration does not meet diagnostic criteria [reference to Simon Broome and DLCN criteria].' [6] DLCN criteria apply to adults only; but Simon Broome does cover children. Simon Broome defines 'definite' FH either as: [6]

- an identified FH variant; or
- raised cholesterol (TC >6.7mmol/L or LDL-C >4.0mmol/L in children) and tendon xanthomas, or evidence of these signs in first- or second-degree relative

Simon Broome defines 'possible' FH as cholesterol above these thresholds combined with family history of raised cholesterol or premature myocardial infarction.

The European Atherosclerosis Society (EAS) similarly state that, for children and adolescents, 'DNA testing establishes the diagnosis,' and consider the detection of a disease-causing variant to be 'the gold standard for diagnosis.'[3] They state there is a 'high probability' of FH in children who have:

- LDL-C above 5.0mmol/L in 2 separate measures despite 3 months' dietary adjustment
- LDL-C above 4.0mmol/L combined with a family history of premature heart disease in a close relative and/or high cholesterol in a parent
- LDL-C above 3.5mmol/L and a parent with an identified disease-causing variant

If a child is known to have 2 parents with HeFH, or has clinical signs of lipid deposition, NICE recommend testing by the age of 5 years if possible.[6] HoFH is diagnosed if a child is found to carry 2 disease-causing variants or, if the child has cholesterol >11mmol/L and either clinical signs or 2 parents with HeFH.[5]

Management of children with FH is usually under the care of a specialist. For HeFH, lipid-lowering therapy is usually considered by the age of 10 years and would be lifelong.[6] Statins are considered first-line; atorvastatin and simvastatin are licensed from 10 years of age, pravastatin from 8 years, fluvastatin from 9 years and rosuvastatin from 6 years. In children who are intolerant of statins, ezetimibe, bile acid sequestrants or fibrates may be prescribed to regulate cholesterol.[6] For children with HoFH, LDL apheresis is the treatment of choice, which removes LDL from the blood. LDL apheresis should be started by 8 years of age and may be considered from the age of 2 years.[5] LDL apheresis is usually combined with lipid-lowering therapy prior to the age of 12 years. Evolocumab, which increases LDL receptors in the liver, is licensed after the age of 12.[5] Liver transplant may also be considered in the management of HoFH.[5, 6]

NICE recommend that liver and muscle enzymes are assessed at baseline prior to starting statins in children. It is also recommended that their growth and pubertal development are monitored routinely.[6]

Positions on universal screening in other countries

In their 2013 consensus statement, the EAS reported that under-diagnosis of FH is a problem, and that, worldwide, most countries have diagnosed less than 1% of affected individuals.[2] Using the lower prevalence estimate of 1 in 500, the country with the highest rate of diagnosis is the Netherlands where it was estimated that 71% of those with FH were diagnosed, followed by Norway at 43%.[2] Both countries perform cascade testing. The UK was ranked fifth with an estimated 12% of people with FH diagnosed using the current system.[2]

In their later 2015 Position Paper on FH in children and adolescents, the EAS stated that FH meets World Health Organisation guidelines for screening being a condition detectable by a simple diagnostic test, that has an asymptomatic stage of disease, where there is an effective treatment, and where case-finding can be made part of routine practice.[3] However, the EAS do not make an explicit recommendation for universal childhood screening. They outline 4 features of 'potential screening strategies' for children or adolescents, given verbatim as below: [3]

- '*if DNA testing is available, cascade screening*[*] *of families is recommended using both a phenotypic and genotypic strategy. If DNA testing is not available, a phenotypic strategy based on country-, age- and gender-specific LDL-C levels should be used*

[*] The term cascade 'testing' has been used in preference to 'screening' in this review, except within quotations

- *children with suspected HeFH should be screened from the age of 5 years; screening for HoFH should be undertaken when clinically suspected (both parents affected or xanthoma present) and as early as possible*
- *age at screening should be similar for boys and girls*
- *universal screening in childhood may also be considered'*

Slovenia is the only country in Europe to have implemented universal childhood screening, since 1995. Total cholesterol is measured at the time of the preschool health check at 5 years of age.[13] Children with a TC of >6mmol/L or 5-6mmol/L and a positive family history are referred to the national lipid clinic. Those with TC 5-6mmol/L and no family history have repeat testing after 6 months and those exceeding 5.5mmol/l or 5-5.5mmol/l with additional risk factors like high BMI are then also referred.[13]

Non-European countries have variably recommended universal screening. Japan reportedly performed universal FH screening in Kumamoto City during the 1990s, but their 2018 guidance states that 'cascade screening is now considered to be a more realistic means of finding FH than universal screening.'[14]

US organisations have taken various positions around screening for FH or dyslipidaemia in general, with some conflicting recommendations, as outlined below.

In 2011 the National Heart Lung and Blood Institute (NHLBI) issued paediatric guidelines for cardiovascular risk reduction. They gave a 'strong recommendation' (one which clinicians should follow) that universal lipid screening should be performed for all children aged 9-11.[15] The guidance advises this as a stable time for lipid assessment as it will precede the onset of puberty in most children. Those with abnormal levels (LDL-C >130mg/dL [3.5mmol/L]) are recommended to have 2 repeat tests over the subsequent months.[15] Notably these recommendations are not purely aimed at identifying children with FH: this is universal child screening for dyslipidaemia (which may or may not be caused by FH) rather than universal child screening for FH *per se*. Neither do the NHLBI give recommendations for the further evaluation of possible FH in screen positives who have raised cholesterol (such as DNA testing). However, they do state that early diagnosis and treatment of FH is part of the rationale for these recommendations.

The National Lipid Association (NLA; 2015)[16] recommended that children aged 2-18 years have lipid screening when: one or both parents have raised cholesterol; there is a family history of premature cardiovascular disease; or where family history is unknown (e.g. an adopted child). They do not specify when testing should be performed within this age group, or whether it is a single test or at regular intervals (they advise lipid screening for adults

every 5 years[17]). However, like the NHLBI, the NLA further recommend universal lipid screening of all children aged 9-11 years, regardless of health or risk factors.[16]

The 2017 guideline from the American Association of Clinical Endocrinologists (AACE) recommended adults are screened for FH if they have either a family history of premature cardiovascular disease, or high cholesterol consistent with FH. They then recommend that 'in children at risk for FH (e.g. family history of premature cardiovascular disease or elevated cholesterol), screening should be at 3 years of age, again between ages 9 and 11, and again at age 18.'[18] Therefore this appears distinct from other recommendations to universally screen all children aged 9-11 years. However, it is not clear from the guideline what FH screening would involve, for example, whether it includes DNA testing.
By contrast the US Preventative Services Task Force (USPSTF) concluded in 2016 that 'the current evidence is insufficient to assess the balance of benefits and harms of screening for lipid disorders in asymptomatic children and adolescents 20 years or younger.'[19] In forming this statement the USPSTF had reviewed evidence on screening for FH, specifically, or wider screening for multifactorial dyslipidaemia.

The Canadian Cardiovascular Society (2018), meanwhile, gives a 'strong recommendation' for the cascade testing strategy.[20] They discuss the US recommendations for universal lipid screening and the UK pilot study of FH screening at the time of routine immunisation. They acknowledge that this could give a higher yield of confirmed cases with the additional opportunity for reverse cascade screening of parents (child-parent screening). However, they state that '[universal] lipid screening remains controversial depending on what level of evidence one views as sufficient.' In this regard they discuss the uncertainty around the diagnostic criteria that should be used for FH in children. They also state that the potential psychological implications of 'labelling' children with diagnosis are unclear. Therefore, Canada gives a 'weak recommendation' that 'universal cholesterol level screening be considered for detection of FH in children with reverse cascade screening of parents when warranted.'[20]

Potential ethical issues and concerns around universal screening

The EAS state that FH meets World Health Organisation criteria for screening.[3] However, the recommended approaches for detection of children with FH clearly vary within Europe and internationally, from opportunistic testing, selective testing of high-risk individuals, cascade testing and universal screening. There appears to be no consensus on the best approach and there is some contention around universal screening for FH in children.

The point has been made that there is ‘clear rationale’ to identify children with FH as early as possible as the atherosclerotic process starts from a young age and may place the individual at increased risk of cardiovascular complications.[4] Statins are well-established as a treatment that can reduce LDL-C and so slow atherosclerosis progression.[4] Then as the EAS state, childhood may be the optimal time to discriminate between raised LDL-C that is caused by FH and non-FH as there is minimal influence from hormones or lifestyle and dietary influences.[3] It is also considered that early diagnosis could help children and their parents make informed decisions around dietary and lifestyle choices and treatment.[21]

However, while there may be clear rationale for treating children with FH who have raised cholesterol and a known disease-causing variant, some sources have raised concerns about the benefit-risk balance of starting statins if children are identified who have only mild or moderately elevated cholesterol.[1, 22, 23] Universal screening may also identify a large proportion of children with polygenic or multifactorial dyslipidaemia, the natural history of which and its distinction from FH, remains unclear.[21, 24] The USPSTF raised concern that most children with this subtype will not progress to a clinically important lipid disorder or develop premature cardiovascular disease and as such could be subject to over-diagnosis.[19] It may be questioned whether it is appropriate to start lifelong treatment from a young age in this group, rather than focus on lifestyle approaches.[25] Concerns are also often raised about the use of statin in children, for example on its longer term safety, including their possible effects on hormone production.[1, 3, 25, 26]

The EAS raised the issue of the psychological consequences of genetic testing and diagnosis with FH, due to the hereditary nature of the condition, lack of early symptoms (for HeFH) and need for long-term lifestyle changes and drug treatment.[3] Another source highlights concern that diagnosing asymptomatic, otherwise healthy young children with a condition that is known to carry future disease risk and prescribing them daily medication could have adverse effects on quality of life.[27] Other potential detrimental effects from screening that have been highlighted include anxiety among children and families, ‘labelling children’, stresses from lifestyle change and the possible contribution to eating disorders.[20, 22] The point has also been made whether a diagnosis of FH could cause difficulties in obtaining life insurance because of the known cardiovascular risk.[21]

A range of studies have looked at the views of child FH screening among people with FH, health professionals and parents. A study in 2019 interviewed 17 UK adults with FH about their views on diagnosing and treating their own children.[28] Around half supported both genetic testing and initiating treatment at a young age as it was protecting their child’s future health. Others voiced numerous concerns including ‘medicalising’, not seeing the urgency of treatment when the child was healthy, concerns the diagnosis may affect the child’s relationship with food, effects on family relationships and health comparisons, and

the long-term safety of statins. [28] An earlier 2008 UK study had also questioned 31 adults with FH.[29] Half had had their children tested and described this as 'unproblematic, obvious and practical'. Only one refused to test their child because they did not want to label them.[29] Another 2008 study from The Netherlands asked 16 children with FH (aged 8-18) about their diagnosis.[30] The children generally understood the condition and its hereditary nature. Half specifically mentioned death as a possible consequence. None reported difficulties taking statins or adapting to lifestyle change, and said the diagnosis did not affect their lives or how they felt. The only concerns expressed were individuals who had known close family members who had died from cardiovascular causes.[30]

These qualitative studies therefore present mixed views among parents, while the study among children with FH suggests they were mostly unaffected by the diagnosis. However, the studies present a very limited perspective. Cultural or societal differences in the Netherlands may affect applicability to the effects on children in the UK. Parental views in the UK relate to diagnosis through the current system of cascade testing and there is need for caution in extrapolating these to potential views around universal screening. However, it is possible that some of the same themes may emerge.

Qualitative studies have also looked at universal screening practice among US practitioners. A 2017 US national survey showed that there had been poor uptake of the recommendations to screen all 9-11 year olds.[31] Most practitioners were still performing selective screening only, on the basis of cardiovascular history or obesity.' The majority were also uncomfortable prescribing statins in this age group.[31] Earlier surveys in specific US regions had revealed similar findings with most performing selective screening and not feeling comfortable managing lipid disorders.[21] It is important to highlight that these views predominantly reflect those of family practitioners rather than specialists. They also relate to universal lipid screening that is not specifically aimed at identifying children with FH, and so may identify several children with lifestyle-related dyslipidaemia.

As identified in the last evidence review, Wald et al[32] in 2011 had conducted a small pilot study to assess the feasibility and acceptability of universal child screening in the UK, which encompassed a child-parent reverse cascade strategy. This study screened 200 children when they attended their routine immunisation at age 15 months. Of 184 parents who completed telephone interviews after they had received the screening results, 98% found screening acceptable and 94% would screen another child. All 7 general practice members involved in the study said that screening was acceptable and would adopt it into their immunisation practice if universal screening were routinely offered.[32] However, none of the children screened positive in this study. Therefore, it is difficult to assess what the opinion of parents and practitioners may have been regarding DNA testing in the case of a positive test result, considering the implications of the diagnosis upon the child's life.

Current UK NSC policy context and previous reviews

The UK NSC does not currently recommend universal screening for FH. This recommendation was made on the basis of the last evidence review on the topic, published in 2016.[7] The last review looked for evidence in relation to universal screening test performance; whether universal screening is effective in reducing mortality and morbidity; the acceptability of screening and treatment to families and clinicians; and the cost-effectiveness of a universal screening programme (principally in comparison with cascade testing/screening).

The 2016 UK NSC[7] review found that the evidence base at that time was insufficient to answer these key questions around universal FH screening in children. The review:

- identified no studies that had examined how well a population-wide screening test for children performed in practice
- found one systematic review of case-control studies which suggested that a screening test for FH may perform best in children between 1–9 years
- identified no studies that assessed whether child screening reduces morbidity and mortality from FH
- found little relevant evidence on the ethical issues and acceptability of universal child screening, including the management of screen-detected children

Objectives

The current update review aims to review and summarise the evidence on universal child screening for FH published since the 2016 external evidence review. It aims to see whether new evidence is available on screening test performance, the mortality and morbidity effects of screening and potential harms, which suggests that the current policy not to offer universal child screening for FH should be reconsidered.

Four questions will be addressed to cover the key issues identified by the last evidence review. These questions are outlined in Table 1.

Table 1. Key questions for the evidence summary, and relationship to UK NSC screening criteria

	Criterion	Key questions	Studies Included
	THE TEST		
5	The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.	1. What are the optimum age and test cut-off values (TC and/or LDL-C concentration [mmol/l]) for screening children for FH?	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.	2. Does universal screening for FH in children reduce FH-related morbidity and mortality in the screened individual?	2
13	The benefit gained by individuals from the screening programme should outweigh any harms for example from over-diagnosis, overtreatment, false positives, false reassurance, uncertain findings and complications.	3. Are there harms from universally screening children for FH?	3

Methods

The current review was conducted by Bazian, in keeping with the UK National Screening Committee evidence review process. Database searches were conducted on 2nd January 2019 to identify studies relevant to the questions detailed in

Table 1.

Eligibility for inclusion in the review

The first 2 questions on test performance and whether universal screening reduces FH-related morbidity and mortality were both assessed by the 2016 external evidence review[7] (search date 2015). As such the evidence for these questions has been reviewed from 2015 onwards. Question 3 on screening-related harms was not assessed by the last evidence review. Therefore the evidence period for this question was extended back to 2008.

The term ‘harms’ is fairly broad and non-specific and may encompass various outcomes related to the screening, diagnostic and management process. Additionally studies containing relevant information on harms may not have this data within the title or abstract. As such it would be difficult to conduct a targeted search back to 2008 for the harms question alone and ensure that all potentially relevant records would be identified. Therefore a broad search was conducted from 2008 onwards that encompassed key terms related to universal child FH screening. This was followed by sifting and full text appraisal to identify:

- studies relevant to questions 1 and 2 from 2015 onwards
- studies relevant to question 3 on harms from 2008 onwards

Questions 2 and 3 on the benefits and harms of screening would also need to look to evidence on the effect of statins in children with FH – regardless of the method of detection and diagnosis. The 2017 Cochrane review[11] was considered to act as the baseline for this evidence. Therefore we additionally conducted a focused search on statins from 2017 onwards to ensure that any later trials were identified.

The systematic literature search of MEDLINE and Embase databases (Embase.com) and The Cochrane Library (Wiley Online) was performed for studies published between January 2008 and January 2019. The full search strategy is presented in 0. The search yielded a total 1344 references following exclusion of 225 duplicates.

The following review process was followed:

1. Each of the 1344 titles and abstract were reviewed against the inclusion/exclusion criteria by one information specialist. 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 information specialist provided input in cases of uncertainty. Any disagreements were resolved by discussion until a consensus was met. A total 439 references were put through at first sift.
2. The 439 references were reviewed in more depth against the inclusion/exclusion criteria by the main reviewer. A total 60 studies were selected for full text appraisal for potential applicability to any of the 3 key questions, which included guidance documents and/or position statements.
3. Each full-text article was reviewed against the inclusion/exclusion criteria by one reviewer, who determined whether the article was relevant to one or more of the review questions. The evidence retrieved and selections for inclusion/exclusion were discussed with a second independent reviewer. Any disagreements were resolved by discussion until a consensus was met.

Eligibility criteria for each question are presented in Table 2 below. Further description of the evidence selection for each key question is presented in the question level synthesis.

Table 2. Inclusion and exclusion criteria for the key questions

Key question	Inclusion criteria							Exclusion criteria
	Population	**Target condition**	**Intervention or Index test**	**Reference Standard**	**Comparator**	**Outcome**	**Study type**	
What are the optimum age and test cut-off values (TC and/or LDL-C concentration [mmol/l]) for screening children for FH?	General child population aged ≤10 years (consecutively enrolled or randomly selected)	FH	TC and or LDL-C to identify FH in asymptomatic children within the specified age group	Combination of TC/LDL-C and family history or identification of an associated gene variant. Other as used by individual studies would be reviewed.	NA	Sensitivity, Specificity, Positive and Negative Predictive Values	Cohorts where all received the index test and reference standard. Systematic reviews (SRs) of these studies.	Opportunistic or selective recruitment. Cascade testing. Case-control studies, non-systematic reviews and editorials, conference abstracts, studies with <20 individuals, non-English language.
Does universal screening for FH in children reduce FH-related morbidity and mortality in	General child population aged ≤10 years for studies of screening vs no screening Children with FH for studies	FH, ideally diagnosed through universal screening	Universal screening Dietary regulation and/or statins for treatment studies	NA	No screening No treatment or later treatment for treatment studies	TC or LDL-C concentration Measure of atherosclerosis (e.g. carotid intima thickness) Cardiovascular morbidity, e.g.	RCTs or SRs of RCTs were prioritised. Comparative cohorts or case-controls	Non-comparative studies, case reports, case series, non-systematic reviews and editorials, conference abstracts,

the screened individual?	of treatment vs no treatment					myocardial infarction Mortality		studies with <20 individuals, non-English language.
Are there harms from universally screening children for FH?	General child population aged ≤10 years for studies of screening vs no screening Children with FH for studies of treatment vs no treatment	FH, ideally diagnosed through universal screening	Universal screening Dietary regulation and/or statins for treatment studies	NA	No screening No treatment or later treatment for treatment studies Non-comparative cohorts reporting harms would also be reviewed	Any harms reported from screening, such as consequences of false positives, false negatives or ambiguous screening test results, psychological consequences. Any treatment-related harms for treatment studies	RCTs or cohorts (comparative or non-comparative) reporting harms of screening or treatment. SRs of these studies.	Case reports, case series or cohorts with <20 individuals, non-systematic reviews and editorials, conference abstracts, studies, non-English language.

Appraisal for quality/risk of bias tool

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

- diagnostic accuracy studies: Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool
- systematic reviews: Critical Appraisal Skills Programme (CASP) Systematic Review Checklist
- cohort studies: CASP Cohort Study Checklist

Results of the quality assessments for each study are presented in the Summary and appraisal of individual studies (Appendix 3).

Question level synthesis

Criterion 5 — the distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.

Question 1 – What are the optimum age and test cut-off values (TC and/or LDL-C concentration [mmol/l]) for screening children for FH?

The 2016 UK NSC review[7] identified one key study relevant to universal child screening for FH. Wald et al (2007)[8] conducted a systematic review of case-control studies in order to determine the cholesterol levels that gave the best discrimination between people with and without FH at different ages. The review included 13 studies in 1,907 people with FH and 16,221 controls. It found that optimal detection of FH was achieved in children of 1–9 years of age, using cut-off thresholds for TC of 1.53 multiples of the median (MoM) and LDL-C of 1.84 MoM, at a fixed false positive rate (FPR) of 0.1%. Two studies had suggested that within the 1–9 age category peak performance may be achieved at 1–2 years of age. On this basis, Wald et al proposed a strategy of universal child screening at the time of the routine immunisation at 1–2 years. This strategy would be a heel prick taken at the time of immunisation, thereby not necessitating a separate screening visit. It would also be a child-parent strategy incorporating reverse cascade testing to identify the affected parent(s).

Wald et al then conducted a pilot study in 2011[32] to assess feasibility and acceptability in 200 children attending a single London general practice (which found no screen positives).

No data on screening test performance was available at the time of the 2016 UK NSC review.[7] However, a large UK cohort study was then in progress to assess the efficacy of this proposed screening programme.

Eligibility for inclusion in the review

This review update assessed whether there was new evidence on the optimum age and test cut-off values (TC or LDL-C) for universal screening of FH in children. The review aimed to identify studies that had enrolled a consecutive or random sample of the general child population. Eligible studies could assess the performance of TC or LDL-C thresholds against a suitable reference standard, such as identification of a disease-causing gene variant and/or repeat TC/LDL-C variants, possibly in combination with positive family history. All children in the cohort would be required to receive both the index test and reference standard.

It was expected that eligible studies may assess either universal child screening only or encompassing subsequent parental screening as part of a child-parent strategy. However, in the case of child-parent screening, this review would focus on the diagnostic performance and outcomes in children only, as a screening programme should primarily be of benefit to the screened individual. Studies in UK settings would be prioritised but screening studies in representative Western populations would also be included.

Studies were reviewed at abstract level, with full text obtained if there was insufficient clarity within the abstract to determine eligibility. The following notable exclusions were applied, either at abstract or full text:

- studies screening groups selected on the basis of risk factors (such as children with diabetes or cardiovascular risk factors)
- studies reviewing the characteristics of children with FH (such as genetic variants) who were diagnosed by universal screening or other strategies but providing no data with which to evaluate screening test performance
- studies evaluating the performance of cascade screening
- studies assessing ways to enhance screening practice or case finding (such as electronic systems in general practice)
- studies evaluating the suitability of diagnostic criteria in adults, such as DLCN score
- studies assessing the analytical validity of different DNA sequencing methods
- case-control studies, which would be expected to overestimate screening test performance
- cost-effectiveness studies
- non-systematic reviews and editorials
- conference abstracts
- publications not available in English language

Description of the evidence

In order to identify all relevant evidence, the literature search for this review was broad using index terms related to child screening for FH and was not targeted by question. A total 60 publications were selected for full text appraisal. All articles were reviewed for potential applicability to any of the 3 questions on universal screening test performance, morbidity effects or harms. Though of these articles, 13 had been selected at abstract level primarily for their potential relevance to this question on test performance.

Two UK studies met inclusion criteria for this question. Wald et al (2016)[9] evaluated the performance of universal child-parent screening using the TC cut-off as informed by their 2007 systematic review.[8] It involved around 10,000 children screened at 1–2 years of age at general practices across the UK. Futema et al (2017)[10] retrospectively evaluated the test

performance of the TC and LDL-C thresholds identified by the 2007 systematic review[8] using blood samples collected from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort at the age of 9 years. The summary of findings from these 2 studies is presented in Table 3 below. A study-level summary of data extracted from each publication is presented in the Summary and appraisal of individual studies (Appendix 3).

Two notable papers were excluded for this key question, both of which relate to the current universal screening programme in Slovenia. Klancar et al (2015)[33] reviewed 272 children who met screening criteria for referral to the national lipid clinic, between 1989 and 2009. FH variants were identified in the *LDLR*, *APOB* or *PCSK9* genes of 57% of children. The remaining 43% of screen positives were diagnosed as having multifactorial hypercholesterolaemia (no children appear to have been considered false positives). Klancar et al estimate that if the prevalence of FH was 1 in 500, the average sensitivity of their screening test was 53.6% over the 5-year period (with an upper peak of 96.3% in 2013). However, if prevalence is 1 in 200 their peak sensitivity would only be 38.5%. As test performance is based on assumed prevalence only, with no follow-up of screen-negatives, this study was excluded.

The later study by Groselj et al (2018)[13] reviewed 170 children fully genotyped between 2012 and 2016. They assessed screening test performance against the 'potential FH population estimated from the National Registry of live-born children' although the authors do not report what they expect the potential population to be (for example, 1 in 200 or 500). They report a wide range of values depending on which criteria were used, reflecting the trade-off between sensitivity and specificity:

- TC cut-off ≥5mmol/L: sensitivity (Sn) 96.7%, specificity (Sp) 8.8%
    - plus positive family history: Sn 55.2%, Sp was 74.7%
- TC cut-off ≥6mmol/L: Sn 78.9%, Sp 62.6%
    - plus positive family history: Sn 50%, Sp 87.9%
- TC cut-off ≥6.7 mmol/L: Sn 52.6%, Sp 91.2%
    - plus positive family history: Sn 35.5%, Sp 97.8%
- TC cut-off ≥8mmol/L: Sn 19.7%, Sp 97.8%
    - plus positive family history: Sn 14.5%, Sp 100%

The Groselj et al[13] study was also excluded as evidence for this criterion due to the assumed (and uncertain) incidence used, with no follow-up of screen-negatives.

Appendix 2 contains a full PRISMA flow diagram (Figure 1), along with a table of the publications excluded at full text appraisal and the reason for exclusion (Table 15. Summary o).

Table 3. Studies evaluating test performance of TC and/or LDL-C thresholds

Study	Design	Population	Index test	Reference standard	Accuracy

Wald et al 2016[9]	Prospective screening cohort, UK
	
	Child immunisation programme, 92 general practices, March 2012 to 2015.
		n=10,095
		Median age 12.7 months
			TC ≥1.53 MoM	**All (screen positives and negatives):**
				FH48 panel of variants
				(46 most common *LDLR* variants, one *APOB* and one *PCSK9* variant)
				Screen positive only:
				If FH48 was negative: DNA sequencing
				If DNA sequencing was negative: repeat blood test at 3 months
				Test accuracy variably assessed by considering FH diagnosis as:
				1 x TC ≥1.53 plus FH48 variant
				1 x TC ≥1.53 plus positive DNA sequence
				2 x TC ≥1.53
				
				(FH48 and DNA sequencing performed using the index heel prick sample)
					92 screen positive:
					• 28 true positive
					  ○ 13 with FH48 variant
					  ○ 7 with variant on DNA sequencing
					  ○ 8 with 2 x TC ≥1.53
					• 64 false positives
					10,003 screen negative:
					• 17 false negative with FH48 variant
					• 9,986 true negative*
					* potential verification bias as screen negatives did not receive DNA sequencing
					Test performance for detection of FH as defined by raised TC and carriage of FH48 variant
					Sensitivity: 43.3%
					Specificity: 99.2%
					PPV: 14.1%
					NPV: 99.8%
					
					Test performance for detection of FH as defined by raised TC and carriage of FH48 variant or another found on DNA sequencing
					Sensitivity: 54.0%*
					Specificity: 99.3%*
					PPV: 21.7%
					NPV: 99.8%*
					* potential verification bias, allowing for this reduces sensitivity to 47% for the same specificity
					
					Test performance for detection of FH as defined by raised TC and variant on FH48 panel or DNA

Study	Design	Population	Index test	Reference standard	Accuracy
					sequence; or 2 samples with raised TC Sensitivity: 62.2%* Specificity: 99.4%* PPV: 30.4% NPV: 99.8%* * potential verification bias, allowing for this reduces sensitivity to 55% for the same specificity

Futema et al 2017[10]	Retrospective cohort, UK
	ALSPAC cohort providing blood samples age 9 years
		n=1,512
		Median age 9.9 years
		
		Drawn from a total number of n=5,083 sampled in the full cohort, where all screen positives (n=15) and a random 30% sample screen negatives (n=1,497) were sequenced.
			TC >1.53 MoM
			LDL-C >1.84 MoM
			(Note, the study reports > rather than ≥)
				Low-read depth whole genome sequencing: screen negatives
				Targeted high-read sequencing of *LDLR*, *APOB* and *PCSK9*: all screen positives and random 4% sample of screen negatives (n=55)
					N=6 children with variants:
					• Using TC >1.53
					  ○ 2 true positive
					  ○ 4 false negative
					• Using LDL-C >1.84
					  ○ 5 true positive
					  ○ 1 false negative
					Test performance of TC >1.53 for carriage of FH variant
					Sensitivity: 33%
					Specificity: 99.1%
					PPV: 13.3%*
					NPV: 99.7%
					*as calculated; study table reports 12.5%
					
					Extrapolating to full cohort (n=5,083) with correction for verification bias:
					Sensitivity: 25%
					Specificity: 99.6%
					PPV: 9.1%
					NPV: 99.9%
					
					Test performance of LDL-C >1.84 for carriage of FH variant
					Sensitivity: 83%
					Specificity: 99.2%
					PPV: 29.4%
					NPV: 99.9%

Study	Design	Population	Index test	Reference standard	Accuracy
					Extrapolating to full cohort (n=5,083) with correction for verification bias: Sensitivity: 62.5% Specificity: 99.8% PPV: 29.4% NPV: 99.9%

Both studies are applicable to the UK population and assess the cholesterol cut-offs for children aged 1–9 years as informed by the 2007 systematic review.[8] Wald et al (2016)[9] is a large cohort study that prospectively assesses the total cholesterol in practice, at the proposed optimum time of 1–2 years. Futema et al[10] applies the same cut-off to historic blood samples collected as part of the ALSPAC cohort when children were 9 years of age, thereby giving disparity between the ages assessed.

Both studies have low risk of bias across most domains of QUADAS-2 (see Appendix 3), except for risk related to the reference standard used. Firstly, both studies have potential verification bias. Secondly, there is the issue of potential incorporation bias, and whether FH would be independently diagnosed by the presence of a disease-causing variant, or whether the cholesterol cut-off itself would be used in diagnosis. How FH would be definitely diagnosed in the context of a universal screening programme is a key issue when interpreting this evidence. These issues, and related test performance, are further discussed below.

Futema et al[10] has high risk of both partial and differential verification bias. Of the full sampled cohort of 5,083, all screen-positives received high-depth targeted sequencing of the 3 principle genes (*LDLR*, *APOB* and *PCSK9*), but only 30% of screen-negative samples (randomly selected) received DNA sequencing (partial verification bias). Furthermore only 4% of this subgroup received the same reference standard as screen-positives. The remainder had low-depth whole genome sequencing which could miss variants compared with targeted high-depth sequencing (differential verification bias). Wald et al[9] had moderate risk of differential verification bias. The full cohort were tested for a panel of 48 of the most common FH variants, but only screen-positives received DNA sequencing if they were FH48-negative. Of 92 screen-positives (TC ≥1.53 MoM), 20 were found to have FH variants and 7 of these were found on DNA sequencing only. It is unclear how many screen-negatives with TC <1.53 MoM may have carried non-FH48 variants. Both studies performed adjusted analyses allowing for limited sequencing of screen negatives, which reduced estimated sensitivity in all analyses (with minimal effect on specificity).

Sensitivity of the TC threshold was poor in both studies. Both studies tested the TC cut-off of 1.53 MoM and found it had low sensitivity between 33% and 54% for identifying children with FH as defined by carriage of an FH-associated gene variant. This was further reduced to 25-47% with adjustment for verification bias. The LDL-C threshold of 1.84 MoM demonstrated much higher sensitivity in the Futema et al[10] study at 83% (reduced to 62.5% with adjustment). However, the LDL-C cut-off was not evaluated by Wald et al.[9] As Futema et al[10] was a retrospective analysis of a smaller sample with only 6 cases, this study alone provides insufficient evidence to be sure that LDL-C measurement would be the preferable screening test.

The PPV of the test was generally very low, below 30% across analyses in both studies. However, this may be a reflection of low prevalence because the test itself has very high specificity. The FPR is less than 1% in all analyses, meaning that among the general child population of young children very few children without FH would have raised cholesterol. Notably, though, the FPR was still higher than the 0.1% rate predicted by the 2007 systematic review.[8] This may because the threshold in the systematic review had been informed by case-control studies where there is greater distinction between values. As Futema et al[10] also considered, the higher FPR in their study could be because they tested samples at the upper boundary of the 1–9 age category. With increasing age there could be greater overlap in cholesterol levels among those with and without FH because of the influence of lifestyle.

The low PPV of the cholesterol cut-off may have limited consequence in terms of false positives if FH was to be definitively diagnosed by the presence of FH-associated variants, which are tested on the same blood sample so would not require recall. However, the important issue appears to be the lack of clarity about how FH should be diagnosed in the context of universal child screening. The TC 1.53 MoM threshold had the best combination of sensitivity and specificity in the Wald et al[9] study when FH was diagnosed as either: a single raised TC in combination with an FH variant; or two sequential blood samples with raised TC. This raises questions as to whether FH should be defined by the presence of associated gene variants or by the presence of raised cholesterol alone.

Wald et al[9] propose that the presence of FH variants alone is insufficient to characterise the FH phenotype. As demonstrated by the low sensitivity, around half of children with FH variants[†] had TC levels below threshold. In Futema et al[10] the majority were below threshold. As Wald et al[9] rightly consider it is the elevated cholesterol that contributes to atherosclerosis in FH. Wald et al[9] state that ‘a person who has [an FH] mutation but does not have a raised cholesterol level is unlikely to have an excess risk of cardiovascular disease.’ They note the variability in cholesterol levels even among people carrying the same FH variant, indicating the role of other factors. They further state that ‘defining [FH] on the basis of a high cholesterol level rather than on the basis of [an FH] mutation acknowledges that [FH] mutations can be benign.’

However, the NICE guideline on FH [6] currently states that ‘all people who have an identified mutation diagnostic of FH have an unequivocal diagnosis of FH even if their LDL-C concentration does not meet the diagnostic criteria.’[6] Simon Broome criteria also consider

[†] 47% using the FH48 panel plus variant found on DNA sequencing, but 57% based on only the FH48 panel, considering screen-negatives did not receive DNA sequencing

that DNA-based evidence alone gives a definite diagnosis of FH. It may therefore be inadvisable to consider a young child carrying an FH variant to be a 'true negative' for the condition because they do not have elevated cholesterol when screened at age 1–2 years. It is possible that cholesterol could increase during later childhood and adolescence. On this basis it may be considered whether 1–2 years is the optimal time to perform screening within the 1–9 age category or whether it may be more beneficial at a later age. Screening at around 9 years of age could give a better indication of whether FH variants are going to raise cardiovascular risk. This would also position screening and diagnosis at the time when treatment (lipid-lowering therapy) could start, rather than screen-detection being far removed from possible treatment. Improved understanding of the genotype-phenotype relationship of different FH variants could also be helpful.

While around half of children with FH variants in the Wald et al[9] study did not have raised cholesterol, almost a third of 'true positives' were considered to have FH on the basis of 2 sequential raised cholesterol samples without an FH variant. This is notably similar to the current Slovenian programme[13, 33] where around 40%‡ of screen-detected children did not have an FH variant and were considered to have multifactorial or polygenic FH. Wald et al[9] consider that 'HeFH, however specified, [should be considered] not as the disorder but rather as a positive screening test for the development of premature cardiovascular disease.' It is an entirely valid point that raised cholesterol is the pertinent risk factor for atherosclerosis. However, this raises the important ethical question on whether it is correct to diagnose a young child with FH on a multifactorial/polygenic basis and start lifelong statins at age 10 years, when the natural history of this condition is poorly understood and concerns have been raised about over-diagnosis.[19] As stated, current criteria consider FH-associated gene variants to give a definitive diagnosis of FH. Simon Broome criteria also consider raised cholesterol to give a definite diagnosis (TC >6.7mmol/L or LDL-C >4.0mmol/L in a child), but only if the child has tendon xanthomas or evidence of these signs in a first- or second-degree relative.[6] 'Possible' FH in a child is also diagnosed on the basis of raised cholesterol, if there is either history of premature myocardial infarction or raised cholesterol in a first or second-degree relative.[3, 6] The strategy proposed by Wald et al[9] involves child-parent screening, therefore the cholesterol levels in parents of children with 2 sequential raised cholesterol samples would be tested. However, the study does not explicitly state whether a child with high cholesterol but no FH variant would be defined as a true positive only if parental cholesterol/family history was compatible with FH.

‡ In the Slovenian programme, disease-causing variants in the *LDLR* or *APOB* genes were not identified for 43% of screen-detected cases who were all termed multifactorial FH. However, within this sample, apolipoprotein E (*ApoE4*) isoforms were identified for just under half, while no variants were detected for the remainder (24% full sample).

To improve screening performance, Wald et al[9] proposed an alternative screening strategy that would involve reducing the TC cut-off to 1.35 MoM with 'reflex' DNA testing (using the same blood sample) of any child above this threshold. This would detect a greater number of children who have FH variants but who do not have excessively raised cholesterol. Test positives for FH would then be considered as children with either TC ≥1.35 MoM plus an FH variant or a 1st and repeat TC≥1.50 MoM. Wald et al[9] applied these thresholds to estimate how many children with FH would be identified when screening a typical population of 10,000 children. However, this new proposed screening protocol has yet to be tested in practice.

Overall these findings give some uncertainty around a potential screening programme in the UK, principally:

- what test and thresholds (TC and/or LDL-C) would be used
- what is the optimal age to screen: 1–2 years or later childhood

what the definitions of true positives and negatives for FH would be: whether an FH variant would give a definite diagnosis (even if cholesterol were below threshold) and whether raised cholesterol alone (multifactorial/polygenic) would establish the diagnosis, or whether a family history/cholesterol levels compatible with FH would be required in these cases

Summary of Findings Relevant to Criterion 5: not met[§]

Two UK studies met inclusion criteria for this question. One large prospective cohort assessed the TC cut-off (1.53 MoM) previously identified to give the best discrimination between children with and without FH, at the time of routine immunisation at 1–2 years. A second UK study retrospectively validated this cut-off using blood samples collected aged 9 years. Both studies found that this TC cut-off had poor sensitivity for identifying children with FH as defined by carriage of an FH gene variant. Around half of children with FH variants had a TC below the cut-off. These would be expected to be false negatives using current diagnostic criteria for FH. Meanwhile almost a third of children detected in the prospective study did not have FH gene variants and were identified on the basis of having two sequential cholesterol samples above threshold (multifactorial/polygenic FH). There is remaining uncertainty over the natural history of this condition, and this could represent a high rate of over-diagnosis in a screening programme. For children with

[§] **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.

raised cholesterol alone, it is unclear whether their parents' cholesterol levels and/or history of premature cardiovascular disease would need to be compatible with FH in order to confirm their diagnosis (thereby meeting Simon Broome criteria for child FH).

The prospective study proposed lowering the TC cut-off to 1.35 MoM and defining FH either as TC above this lower threshold plus an FH variant (improving sensitivity), or a first and repeat TC≥1.50 MoM at age 1–2 years. However, this has to be tested in practice. Another option may be to raise the screening age and/or use LDL-C as the test rather than TC. The retrospective study found the best combination of sensitivity and specificity when using the LDL-C cut-off (1.84 MoM) at 9 years. Screening at age 9–10 years could potentially give a better indication of whether FH variants are going to raise cholesterol/cardiovascular risk. This could also have the benefit of placing diagnosis at the time when treatment could start, which is relevant in the context of a screening programme. However, as this was a retrospective analysis based on few cases, more evidence is needed to confirm this as the appropriate age for a screening programme and LDL-C as a preferable test.

On the basis of the remaining uncertainties around the optimal screening age, test marker and cut-off to use, and how FH should be definitively diagnosed in a universal child screening programme, this criterion is not met.

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

Question 2 – Does universal screening for FH in children reduce FH-related morbidity and mortality in the screened individual?

The 2016 UK NSC review[7] identified no randomised controlled trials, or prospective or retrospective controlled studies, that had assessed the effect of universal screening in children on FH-related morbidity and mortality. It was expected that this may be because of the long duration of follow-up that would be required to look at cardiovascular outcomes and mortality following universal screening.

Eligibility for inclusion in the review

This review update assessed whether there was new evidence that universal child FH screening reduces disease-related morbidity or mortality. The primary aim was to identify either randomised controlled trials (RCTs) or controlled studies comparing outcomes in child populations receiving universal FH screening with no screening. Eligible studies could look at change in cholesterol levels or intermediate measures of atherosclerosis in children (such as increased carotid intima thickness), or cardiovascular-related morbidity or mortality in older adolescents/adults.

Initiation of lipid-lowering therapy is the main reason why screening could be expected to affect the morbidity and mortality of indivdiuals with FH. Therefore, in the absence of studies comparing screened and non-screened populations, the secondary aim was to look at the effect of lipid-lowering therapy in children with FH (identified by any means) compared with placebo/no treatment or other management, such as lifestyle adjustment. In this regard, a 2017 Cochrane review[11] on statins in children with FH had been identified at the scoping stage. The earlier 2014 version of this Cochrane review had informed the current NICE guideline recommendations around treatment of children with FH.[6] Therefore it was expected *a priori* that this 2017 Cochrane review would form the baseline evidence for the secondary question on the effects of statins in children with FH. A targeted supplementary search was conducted for papers published 2017-19 to ensure that any subsequent RCTs of statins in children were identified.

Studies were reviewed at abstract level, with full text obtained if there was insufficient clarity within the abstract to determine eligibility. The following notable exclusions were applied, either at abstract or full text:

- non-comparative studies reporting the clinical characteristics of a cohort of children with FH but not comparing screening vs no screening or treatment vs no treatment

- studies comparing cholesterol levels or morbidity outcomes in children with FH compared to children without FH
- RCTs of statins in children with FH conducted 2015-16 (that would have been eligible for the 2017 Cochrane review)
- systematic reviews of statins pre-dating the 2017 Cochrane review
- small cohorts or case series including <20 participants
- case reports
- non-systematic reviews and editorials
- conference abstracts
- publications not available in English language

Description of the evidence

In order to identify all relevant evidence, the literature search for this review was broad using index terms related to child screening for FH and was not targeted by question. A total 60 publications were selected for full text appraisal and all were reviewed for their potential applicability to any of the 3 questions on test performance, morbidity effects or harms. Twelve articles were selected primarily for their potential relevance to this question on morbidity, though similarly these studies were expected to have potential cross-applicability to question 3 on harms.

Effects of universal screening

No studies were identified that had compared morbidity or mortality outcomes (or intermediate indicators) between populations identified through universal child screening compared with no screening.

One systematic review met the inclusion criteria for the primary focus of the question on the morbidity/mortality effects of universal screening. The USPSTF systematic review on lipid screening in childhood and adolescence for the detection of FH[19, 23, 34] looked for studies published from January 2005 up to April 2016 on two key questions relevant to this current update review:

1. Does screening for FH in asymptomatic children or adolescents delay or reduce the incidence of myocardial infarction or stroke in adulthood?
2. Does screening for FH in asymptomatic children or adolescents improve intermediate outcomes (i.e. reduce lipid concentrations or reverse or slow the progression of atherosclerosis) in childhood or adolescence?

The USPSTF review identified no evidence for these two key questions, either for universal or selective screening.

The USPSTF review covers only a small period of time (January 2015 to April 2016) covered by this evidence review update (January 2015 to January 2019). However, this confirms the findings of this rapid review search that no evidence is available for this key question.

Effects of treatment

One study met inclusion criteria for the secondary part of this question looking at the morbidity/mortality effects of treatment in children with FH. The Vuorio et al (2017)[11] Cochrane review assessed the effects of statins in children with FH. The summary of findings from this study is presented in Table 4 below. Of note the USPSTF review also assessed the benefits and harms of treating FH, but the Cochrane review had a later search date and was selected in preference.

No subsequent RCTs of statins published 2017-19 met the inclusion criteria. However, one additional study was identified that was not prioritised for inclusion. This was an RCT[35] assessing statins in 14 children with HoFH. This study would normally be excluded on the basis of its small size, including fewer than 20 participants. However, as HoFH is rare (estimated prevalence 1 in one million), trials in children with HoFH are inevitably small. This study essentially shows that statins can reduce cholesterol in this population. It is summarised in Table 5 at the bottom of this section but does not form part of the main evidence for this key question.

No RCTs or comparative studies of other lipid-lowering therapy were identified from 2015 to 2019.

No evidence was identified assessing the effect of dietary or lifestyle approaches.

Therefore 2 publications met inclusion criteria for this key question. The ‘Summary and appraisal of individual studies’ (Appendix 3) contains a study-level summary of data extracted from the USPSTF[19, 23, 34] and Vuorio et al (2017)[11] systematic reviews.

Appendix 2 contains a full PRISMA flow diagram (Figure 1), along with a table of the publications excluded at full text appraisal and the reason for exclusion (Table 16).

Discussion of findings

Effects of universal screening

No evidence was identified to inform whether universal screening for FH in children affects FH-related morbidity or mortality, either when looking at intermediate or longer term outcomes.

Effects of treatment

Table 4. Effect of statins on FH-related morbidity

Study	Design and aim	Included studies	Morbidity-related outcomes
Vuorio et al (2017)[11]	Cochrane SR Aim: to assess the effectiveness and safety of statins in children aged ≤18 years with HeFH. Search February 2017.	9 RCTs (n=1,177) Variable statins and dose, intervention and follow-up duration range 6 weeks to 24 months (median 24 weeks). Publication 1996 to 2015. 6/9 studies multicentre; all representative of Western populations. Age range: 3 studies 10-17 and one study each of 6-17, 8-16, 8-17, 8-18, 11-17 and 11-18.	**Moderate quality evidence that statins reduce LDL-C compared with placebo at up to 1 year** Mean difference (MD): -32.15% (95% CI -29.40 to -34.90%) (6 studies, n=669, I^2 =89%) Also significant reduction in LDL-C at all time-points of 1 month (3 studies), 6 months (4 studies) and 1 year (2 studies) **Statins reduce TC and increase HDL-C compared with placebo at up to 1 year (not graded outcomes)** TC reduction: MD -26.53% (95% CI -28.54 to -24.51%) (6 studies, n=669) HDL-C increase: MD +3.11% (95% CI +0.55 to +5.67%) (6 studies, n=669) Triglycerides, no effect: MD -3.27% (95% CI -12.03 to +5.50%) (5 studies, n=525) **Low quality evidence that statins reduce carotid intima media thickness at up to 2 years** MD: -0.01mm, 95% CI -0.03 to -0.00mm (1 study, n=211) **Low quality evidence that statins improve endothelial function at up to 1 year** Absolute change 2.70% increase with statins (95% CI 0.42 to 4.98%) vs 1.2% change with placebo (95% CI not reported) (1 study, n=50)

Vuorio et al[11] was a comprehensive, high quality systematic review that is expected to have identified all relevant trial RCT evidence on the morbidity-related effects of statins in children and adolescents with FH (heterozygous). Across the 9 studies it was uncertain whether there could be risk of bias related to method of randomisation/allocation and

selective or incomplete outcome reporting. However, overall these risks were thought to be negligible and the identified studies were of good quality.

Change in LDL-C level was the primary outcome of the review. There is moderate quality evidence that statins reduce LDL-C in children with FH in the short to medium term at up to one year. Similar beneficial effects were found for reduction in TC. There was high heterogeneity in the size of effect between studies, which is expected to be due to differences in the statin and dose used. No studies had looked at the sustained effectiveness of statins in reducing LDL-C/TC in the longer term beyond one year.

It may be expected that reduction in LDL-C (particularly if sustained) would reduce the risk of atherosclerosis and associated morbidity. However, there is very limited, low quality evidence to inform this. The Cochrane review identified one study that showed that statins can reduce thickness of the carotid intima-media (CIMT). Another small study subgroup suggested that statins may reduce endothelial dysfunction. Both are considered to be intermediate markers of atherosclerosis and predictors of later cardiovascular disease. While this is in keeping with the known effects of statins in adults, these 2 studies of small sample size cannot provide strong evidence for this benefit of statins in children with FH.

Similarly there is no evidence available to inform whether statins started in childhood or adolescence can reduce cardiovascular-related morbidity (such as myocardial infarction or stroke) or mortality in adulthood. This is might bedue by the long follow-up required making such studies less feasible.

The Cochrane review is not able to inform the optimal statin or dose to use, or the optimal age for starting treatment. Neither was it able to analyse whether the effect of statins differs according to baseline TC/LDL-C level or the specific criteria used to diagnose FH.

This latter point is of particular importance when considering the applicability of this evidence. Studies eligible for inclusion in the Cochrane review had to have diagnosed child FH either by the presence of an FH variant alone, or using clinical criteria (TC above the age-adjusted upper limit plus hypercholesterolaemia in a parent). NICE have applied the evidence from this Cochrane review (2014 publication) to inform the treatment of children with FH who are diagnosed with FH either clinically (cholesterol, clinical signs and/or compatible parental signs) or by the presence of an FH variant alone (through cascade testing). A universal screening programme could detect such children, and statin treatement is expected to be beneficial for them, even given the lack of direct evidence that it improves long-term morbidity and mortality.

However, as evident from Criterion 5, about a third of children detected through universal screening could potentially be diagnosed with multifactorial/polygenic FH on the grounds of raised cholesterol alone. The screening studies did not indicate whether parental cholesterol, clinical signs or history of cardiovascular disease would need to taken into account to confirm the diagnosis of FH in these cases. There is no evidence available to inform whether starting lifelong statin treatment is beneficial for young children with raised cholesterol alone.

Table 5. Non-prioritised study looking at the effect of statins in HoFH

Study	Population	Intervention	Comparator	Morbidity-related outcomes
Stein et al (2017) **Multicentre crossover RCT**	N=14 with HoFH aged 6-17 years	Rosuvastatin 20mg for 6 weeks (then crossover to placebo) Preceded by 4 week lead-in (10mg), and followed by 12 week maintenance (20mg)	Placebo for 6 weeks (then crossover to intervention)	Statin reduced LDL-C vs placebo Absolute reduction -85.4mg/dL MD -22.3% (95% CI -33.5 to -9.1%)

Summary of Findings Relevant to Criterion 11: Criterion not met**

There is no evidence available to inform whether universal screening for FH in childhood reduces FH-related morbidity and mortality. No comparative studies have compared cholesterol levels, intermediate markers of atherosclerosis or longer-term cardiovascular outcomes between screened and non-screened populations of children.

One systematic review provides moderate quality evidence that statin treatment in children or adolescents diagnosed with HeFH reduces LDL-C and TC in the short to medium term at up to one year. It found limited, low quality evidence that statins in children may reduce intermediate markers of atherosclerosis (CIMT and endothelial dysfunction) at up to 2 years. No information was available on the effect on cholesterol levels or cardiovascular outcomes in the longer term.

The evidence cannot inform the optimal statin, dose or age to start treatment, or whether statins may have different effect according to baseline LDL-C/TC level or the criteria used

** **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.

to diagnose FH. A universal screening programme would identify children with FH who may otherwise have been detected clinically or through the cascade testing system. For these children, starting statin treatment is expected to be beneficial, even given the lack of evidence around longer term effects. However, there is no evidence to inform whether starting lifelong statin treatment is beneficial for children who are diagnosed with multifactorial/polygenic FH on the basis of raised cholesterol alone.

In summary, no evidence has assessed whether universal screening affects FH-related morbidity or mortality compared with no screening. There is adequate evidence that statins reduce LDL-C and TC levels at fup to one year in children meeting diagnostic criteria for FH. Even given the lack of direct evidence that this reduces FH-related morbidity in the longer term, treatment is expected to be beneficial for this group. The management of children with multifactorial/polygenic FH is, however, unclear. On this basis, this criterion is not met.

Criterion 13 — the benefit gained by individuals from the screening programme should outweigh any harm, for example from over-diagnosis, overtreatment, false positives, false reassurance, uncertain findings and complications.

Question 3 – Are there harms from universally screening children for FH?

European and international countries have taken variable approaches towards identifying children with FH (or dyslipidaemia in general) including universal screening, cascade and selective testing, with no clear consensus on approach. As discussed, a number of concerns have been raised around universal screening. These include the potential psychological and quality of life effects from diagnosis, lifestyle adjustment and treatment from a young age. There had been concerns whether universal screening could result in over-diagnosis and detection of mildly-elevated cholesterol levels (notably not the case in the UK screening cohort, where all screen-positives had by definiton raised cholesterol) or multifactorial/polygenic FH that might not progress to clinically significant atherosclerosis. There have been also widespread concerns about the long-term safety of statins in children, including potential effects on growth and puberty, risk of liver dysfunction and myopathy.[1, 3, 11, 25, 26]

The 2016 UK NSC review[7] did not specifically address harms from screening, but had reviewed whether universal screening would be clinically, socially and ethically acceptable to professionals and to the public. The review found limited evidence in this regard. The Wald et al pilot (2011)[32] had reported that of 184 (92%) of parents who responded to interviews, 98% said they found screening acceptable and 94% would have another child screened. All participating practitioners found screening acceptable. However, this gave a limited perspective; views were not explored further, and no child with FH had been detected by screening which may have given a different perspective.

In light of the lack of consensus and concerns raised around universal screening, the update review aimed to explore this issue further and look beyond acceptability alone to see whether there are any harms from universally screening children for FH.

Eligibility for inclusion in the review

This review update assessed whether there is evidence that universal child FH screening is associated with any harms. As this question was not specifically assessed in the last 2016 review, the search period was extended back to 2008. The review aimed to identify any RCTs or cohort studies (comparative or non-comparative) that assessed harms from universal screening. Harm is a non-specific term and could encompass any perceived or actual adverse effects from any aspect of the full screening programme, including diagnosis

and management (lifestyle or medication). Studies would not necessarily have to identify harms (studies finding no harms from universal screening would be equally eligible) but they would need to report some form of assessment or follow-up to see if there were adverse effects. Studies containing information on views or acceptability of universal screening were also identified.

As harms from screening could largely be treatment-related, in the absence of studies in universally-screened populations, the secondary aim was to look at harms from lipid-lowering therapy or lifestyle approaches in children with FH (identified by any means). Such studies could compare treatment with placebo/no treatment/alternative treatment or early with late treatment.

As for question 2 on the morbidity/mortality effects of screening, the 2017 Cochrane review[11] on statins in children with FH had been identified at the scoping stage. It was expected *a priori* that this 2017 Cochrane would form the baseline for RCT evidence on the adverse effects of statins in children with FH. A targeted supplementary search was conducted for papers published 2017–19 to ensure that any subsequent RCTs of statins in children were identified. The reviewers also looked back to 2008 to identify any cohorts reporting adverse effects from statins in children with FH, as cohorts may not have been considered for the 2017 Cochrane review.

Studies were reviewed at abstract level, with full text obtained if there was insufficient clarity within the abstract to determine eligibility. The following notable exclusions were applied, either at abstract or full text:

- studies reviewing the harms of, or views on, non-universal screening strategies, such as cascade testing or selective screening
- studies reporting the clinical characteristics of children with FH, or the adverse health effects from the condition, but not relating this to screening or treatment
- studies comparing the health outcomes and indicators of atherosclerosis in children with FH compared to children without FH
- RCTs of statins in children with FH conducted 2015-16 (that would have been eligible for the 2017 Cochrane review)
- systematic reviews of statins pre-dating the 2017 Cochrane review
- RCTs or cohorts reporting the adverse effects of statins that were not, or not exclusively, carried out in populations of children diagnosed with FH
- small cohorts or case series including <20 participants
- case reports
- non-systematic reviews and editorials
- conference abstracts
- publications not available in English language.

Description of the evidence

As described in order to identify all relevant evidence, the literature search for this review was broad using index terms related to child screening for FH, and was not targeted by question. A total 60 publications were selected for full text appraisal on the basis of their potential applicability to universal screening strategies for FH or related treatment. All of these articles were reviewed for any potential content related to harms or adverse effects from screening or treatment.

Harms from universal screening

No studies were identified that reported on universal screening programmes or pilots and reviewed their associated harms or adverse effects (or lack of them).

The Wald et al (2016)[9] cohort trialling child-parent screening at age 1–2 years in the UK provided limited information for this question. The study reported that of 37 children identified to have an FH gene variant, 32 pairs of parents accepted genetic testing themselves (5 parents declined/were unavailable). Twenty-five of 28 parents who tested positive subsequently started statin treatment. Wald et al report that of these test-positive parents 'all indicated that they thought the screening was worthwhile and none reported negative effects.' However, there is no further information than this. It is unclear whether these views relate to their child being screened, or to the parents themselves being identified as carriers of an FH-variant and being given the option of starting statins. Views on the care and potential treatment of their child were not explored. Neither were views reported for the 4/32 parents whose child apparently tested positive for an FH variant when they did not, nor for the 5/37 parents who declined testing themselves or were unavailable. The study does not report views for the parents of 8 children who had 2 sequential raised cholesterol samples but no identified FH variant. Related to this, neither are the views explored for the 64 children who were recalled for a repeat blood test but found to screen negative (cholesterol below threshold) on the second occasion. The study further reported that screening had no effect on immunisation rates (76% uptake in the year before screening and 85% after the second year). However, potential adverse effects were not explored beyond this.

Various publications were identified that reported potential concerns and controversy around universal screening, as covered in the background section of this review. However, these tended to be opinion or based on non-systematic review on the topic citing, for example, selected studies or commentaries. Additionally, various qualitative studies were identified that assessed parental views on cascade testing, or the views of US practitioners towards the NHLBI and NLA recommendations to screen all children for dyslipidaemia.

These studies are also discussed in the background section to this review, but do not provide evidence for the question on harms of universal child FH screening.

One study met the inclusion criteria for the primary focus of the question on the harms of universal screening: the USPSTF systematic review on lipid screening in childhood and adolescence for the detection of FH.[19, 23, 34] This systematic review looked for studies published from January 2005 up to April 2016 on the key question 'What are the harms of screening for FH in children and adolescents?'

The USPSTF review identified no evidence for this question, either for universal or selective screening strategies. Therefore, this provides support for the finding of this rapid review search that no evidence is available for the harms of universal FH screening in children.

Harms from treatment

Two studies met the inclusion criteria for the secondary part of this question looking at treatment harms. The Vuorio et al (2017)[11] Cochrane review assessed the adverse effects of statins in children with FH. Humphries et al (2018)[12] reviewed the UK Paediatric FH Register to look for signs of liver or muscle toxicity in children treated with statins and comparing growth outcomes between treated and non-treated children. A summary of findings from these 2 studies is presented in Table 6 below.

No further studies met inclusion criteria for this key question, though several other studies were worthy of note. Four non-comparative cohorts assessed the safety of statins in children with HeFH. Two of these reported longer term follow-up of one of the 9 RCTs included by the Cochrane review. The remaining 2 studies were regional cohorts of treated children. These studies essentially support the safety of statins in the medium to long-term.

A further 2 studies assessed the safety of treatment in children with HoFH. One was the small RCT[35] of statins (n=14) mentioned in question 2. The second was a systematic review including case series and case reports of lipoprotein apheresis. The current evidence review update excluded RCTs with fewer than 20 participants, case reports and case series. However, as HoFH is rare (estimated prevalence 1 in one million), studies in children with HoFH are inevitably small, and so these findings have been noted.

These 6 non-prioritised studies are briefly summarised in Table 7 at the bottom of this section, but they do not form part of the main evidence for this key question.

Therefore, in total, 3 publications met inclusion criteria for this key question. The ‘Summary and appraisal of individual studies’ (Appendix 3) contains a study-level summary of data extracted from the USPSTF[19, 23, 34] and Vuorio et al (2017)[11] systematic reviews and the UK Paediatric FH Registry review.[12]

0contains a full PRISMA flow diagram (

Figure), along with a table of the publications excluded at full text appraisal and the reason for exclusion (Table 15. Summary o)

Discussion of findings

Harms from universal screening

No evidence was identified to inform whether or not universal screening for FH in children is associated with any harm.

Harms from treatment

Table 6. Effect of statins on FH-related morbidity

Study	Design and aim	Included studies/population	Harms-related outcomes
Vuorio et al (2017)[11]	Cochrane SR Aim: to assess the effectiveness and safety of statins in children aged ≤18 years with HeFH. Search February 2017.	9 RCTs (n=1,177) Variable statins and dose, intervention and follow-up duration range 6 weeks to 24 months (median 24 weeks). Publication 1996 to 2015. 6/9 studies multicentre; all representative of Western populations. Age range: 3 studies 10-17 and one study each of 6-17, 8-16, 8-17, 8-18, 11-17 and 11-18.	**Moderate quality evidence that statins do not increase the risk of adverse effects at up to 1 year compared with placebo** Total 402/1000 events vs 399/1000 placebo (Risk Ratio [RR] 1.01, 95% Confidence Interval [CI] 0.81 to 1.26) (2 studies, n=276) Also no effect at: • 1 month: RR 0.86 (95% CI 0.65 to 1.13) (2 studies, n=248) • 6 months: RR 1.02 (95% CI 0.82 to 1.27) (3 studies, n=416) **Low quality evidence that statins do not increase the risk of liver toxicity at up to 2 years compared with placebo** Risk of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevation >3x upper limit of normal • 1 month: AST and ALT (RR 0.00, 95% CI 0.00 to 0.00) (2 studies, n=175) • 6 months: AST (RR 2.40, 95% CI 0.29 to 19.85) and ALT (RR 2.03, 95% CI 0.24 to 16.95) (4 studies, n=538) • 1 year: AST and ALT (RR 2.03, 95% CI 0.08 to 49.09) (2 studies, n=254) • 2 years: AST (RR 0.21, 95% CI 0.01 to 4.23) and ALT (RR 0.00, 95% CI 0.00 to 0.00) (1 study, n=211) Based on 4 cases each of AST and ALT elevation in the statins group vs 2 cases of AST elevation in the placebo group (no cases at one month) (total 7 studies, n=924)

Study	Design and aim	Included studies/population	Harms-related outcomes
			Low quality evidence that statins do not increase the risk of myopathy at up to 1 year compared with placebo Risk of creatinine kinase (CK) elevation >10x upper limit of normal • 1 month: RR 3.23 (95% CI 0.18 to 58.84) (3 studies, n=330): • 6 months: RR 0.22 (95% CI 0.01 to 5.28) (2 studies, n=229) • 1 year: RR 0.67 (95% CI 0.04 to 10.57) (2 studies, n=254) Based on 5 cases of CK elevation in the statin group vs 2 in the placebo group (total 6 studies, n=669) **Low quality evidence that statins do not affect the chance of reaching puberty by 2 years compared with placebo** • 6 months: RR 0.99 (95% CI 0.66 to 1.50) (2 studies, n=355) • 1 year: RR 0.89 (95% CI 0.51 to 1.54) (1 study, n=139) • 2 years: RR 0.95 (95% CI 0.77 to 1.18) (1 study, n=211) **No evidence on quality of life effects**
Humphries et al (2018)[12]	Review of the UK Paediatric FH Register (established 2012)	N=300 children with HeFH: n=135 (45%) treated with statins vs n=165 untreated Characteristics significantly different between treated vs untreated (p≤0.05): • Age (mean 10.7 vs 9.5 years) • Family history of heart disease (43.7% vs 32.7%) • TC (mean 7.79 vs 7.15mmol/l) • LDL-C (mean 5.88 vs 5.21mmol/l) • Weight (mean 42.1 vs 37.4kg) • Height (mean 1.45 vs 1.37m)	Mean follow-up 2.7 years **No within-person sign of liver toxicity or myopathy (before statins vs follow-up)** Mean change from baseline: • ALT (n=97): +1.61 U/L (95% CI 0.10 to 43.11), *p=0.008** • AST (n=25): +0.52 U/L (95% CI -1.85 to +2.89), p=0.26 • CK (n=65): +7.6 U/L (95% CI -2.33 to +17.63), p=0.39 * No sign of toxicity for any measure as indicated by elevation >2.5 times the normal range. **No effect on growth (treated vs non-treated)** Mean change with adjustment for age and sex: • Weight (n=80 statins vs n=65 no statins): +3.58kg vs +3.53kg, p=0.91 • Height (n=64 statins, n=46 no statins): +4.45cm vs +4.60cm, p=0.73

Both the Cochrane review and analysis of the UK Paediatric FH register have consistent results. They find no evidence that statins are associated with risk of adverse effects, liver toxicity, myopathy or effects on growth and maturation in the short to medium term at up to 2 years. However, there is limitation to the size and strength of this body of evidence.

Vuorio et al[11] was a comprehensive and high quality systematic review that is expected to have identified all relevant trial RCT evidence on statins in children and adolescents with FH (heterozygous). Overall the risk of bias across the identified studies was thought to be minimal. The best evidence available was for adverse effects at up to one year, which was graded as moderate quality. Adverse effects were common, equally reported by 40% of both statin and placebo groups. However, reporting of adverse effects was not standardised across studies and is not further defined in the review. Therefore, it is uncertain what may have been included in this outcome. Statins were not associated with risk of liver toxicity and myopathy as measured by enzyme change, though this is low quality evidence. There were few events in these relatively small studies and most confidence intervals were very wide indicating the high degree of uncertainty. Similarly, evidence that statins do not affect onset of puberty was low quality.

The UK registry review[12] supports the finding that statins are not associated with liver toxicity or myopathy in the individual. It also finds no difference in growth between treated and untreated individuals. However, this data is observational and dependant on what is recorded in the registry. Notably assessments of biochemistry or growth measures often appear to be based on a low proportion of those treated in the whole cohort (for example, repeat AST measures only available for 25/135 started on statins). The reason for this is not given in the paper and it is uncertain whether it could affect the reliability of analyses.

Other limitations to the strength and applicability of the evidence are common to both studies. All adverse effects have only been assessed in the short to medium term for around 1–2.5 years, on average. Though there is no evidence to suggest harms of statins, it is not possible to exclude the possibility of longer term effects. Though 10-year follow-up was performed for one of the RCTs in the Cochrane review[11] (Table 7) this does not provide comparative evidence between treated and non-treated populations. There are also gaps in the outcomes assessed. For example, the included studies have not assessed quality of life, neurological or cognitive effects, effects on glycaemic control, and as yet there is limited evidence for hormonal effects and later fertility. Neither can the findings inform the safety of specific statins, doses or age at treatment initiation.

In summary, though there is a lack of information on some potential harms and longer term effects, there is no evidence that statins are associated with any harms for children with FH up to the longest follow-up period (around 2.5 years). However, it is important to consider

who this evidence is applicable to. The Cochrane review[11] covers children with FH who were diagnosed on the basis of an identified gene variant alone, or raised cholesterol in combination with hypercholesterolaemia in a parent. The registry study[12] directly represents children with FH currently being treated in the UK, who have mostly been identified through cascade testing. As such it is uncertain whether these populations could have characteristic differences, such as baseline cholesterol level or a greater proportion carrying FH gene variants, than may be identified through universal screening. The evidence cannot inform the risk-benefit balance of starting statin treatment in young children who are defined as having multifactorial/polygenic FH on the basis of raised cholesterol alone. As said, in the context of a universal screening programme, it is unclear whether parental signs or medical history would need to be compatible with FH in order to confirm a clinical diagnosis of FH in such cases.

The UK registry study[12] identified 102 children aged over 10 years who had not been started on statins. In 37% of these cases it was said to be because the physician considered the child to be at low risk and in 13% because the patient or their parent/carer declined treatment. Again, this applies predominantly to children diagnosed through cascade testing. However, it demonstrates some potential reluctance to treat which may be because of safety concerns or views that the individual child is not at raised cardiovascular risk despite diagnosis of FH.

Finally of note, no studies were identified investigating the potential adverse effects of lifestyle approaches. There is also limited evidence for the effects of alternative treatment. However, only 2% in the UK FH registry were documented to have received alternative treatments, and so statins remain the mainstay of treatment in children and adolescents.

Table 7. Non-prioritised studies looking at the adverse effects of treatment for HeFH or HoFH

Study	Population	Intervention	Comparator	Harms-related outcome
HeFH				
Braamskamp et al (2015)[36] **Follow-up of RCT (included by Vuorio et al)**	N=205 96% of n=214 eligible	Pravastatin (<14 years, 20mg; ≥14 years, 40mg)	None (placebo group switched to the statin after the 2 year trial)	**10 year follow-up** Adverse effects (AEs) reported: n=40 (19.5%), mostly muscle aches (n=19, 9.3%) and gastrointestinal symptoms (n=14, 6.8%) No serious AEs Discontinuation due to AEs: n=3 (1.5%) Overall statin adherence: n=148 (78.7%)
Braamskamp et al (2015)[37] **Follow-up of RCT (included by Vuorio et al)**	N=88 41% of n=214 eligible following exclusion of those on oral contraceptives and non-adherent to statins	Pravastatin (<14 years, 20mg; ≥14 years, 40mg)	N=62 unaffected siblings	**10 year follow-up** Hormone levels of testosterone (males), estradiol (females), luteinizing hormone (LH) and follicle-stimulating hormone (FSH) all within the reference range. No difference from siblings
Carreau et al (2011)[38] **2 centre cohort, France.**	N=185 Mean age at treatment initiation: 11 years	Pravastatin variable dose)	None	**2.2 year follow-up** AEs reported: n=24 (13%) Of these n=8 experienced asymptomatic, mild CK elevation, n=10 reported muscles aches without CK elevation, n=2 muscle aches with moderate elevation: all resolved either spontaneously or with change of statin No effect on growth or puberty
Araujo et al (2016)[39] **Single centre cohort, Argentina.**	N=78 Mean age at treatment initiation: 9.3 years ezetimibe and 11 years statins	Combined therapy: Ezetimibe (<10 years, 5mg; ≥10 years, 10 mg). Atorvastatin added if goals weren't achieved (<10 years, 2.5mg; ≥10 years, 5mg).	None	**2.8 year follow-up** Ezetimibe only: n=1 reported headache Statin addition: n=2 asymptomatic CK elevation, n=3 muscle aches and CK elevation (none >2x level) No change in other laboratory parameters No effect on growth or puberty
HoFH				

Study	Population	Intervention	Comparator	Harms-related outcome
Stein et al (2017)[35] **Multicentre crossover RCT**	N=14 with HoFH aged 6-17 years	Rosuvastatin 20mg for 6 weeks (then crossover to placebo) Preceded by 4 week lead-in (10mg), and followed by 12 week maintenance (20mg)	Placebo for 6 weeks (then crossover to intervention) Preceded by 4 week lead-in (10mg), and followed by 12 week maintenance (20mg)	**28 weeks total follow-up** No elevations AST, ALT or CK >2x level Overall AEs low: lead-in (n=3), crossover (n=1 statin and n=4 placebo), maintenance (n=1) No serious AEs
Luirink et al (2018)[40] **Systematic review**	35 studies reporting adverse effects in n=115 people aged ≤18 years Represents 46% of total 76 studies (n=209) identified (45 case series, 31 case reports) published 1978-2018 across 17 countries Mean age treatment 9.3 years.	Lipoprotein apheresis	None	**Follow-up variable (1-20 years)** 9.6% (n=11) excluded from analysis as detail was not given on the specific mode of treatment delivery. Remaining 104: 61.5% (n=64) experienced ≥1 AE: biochemical abnormalities mostly iron deficiency (18.3%), gastrointestinal (17.3%), vascular access problems (17.3%), hypotension (15.4%), allergic reactions (16.3%) and fatigue (4.8%)

Summary of Findings Relevant to Criterion 13: Criterion not met††

There is currently insufficient evidence to inform whether or not universal screening for FH in childhood may be associated with harm. No studies of universal screening programmes have performed follow-up to see whether any aspect of the screening, diagnosis and management process may be associated with any adverse effects.

One systematic review provides moderate to low quality evidence that statins in children/adolescents diagnosed with HeFH are not associated with increased risk of adverse effects, liver toxicity, myopathy or effects on onset of puberty in the short to medium term at up to 1–2 years. This is supported by data in the UK Paediatric FH Registry. Longer term safety information remains unavailable. There is also no data on other outcomes of potential relevance including quality of life, neurologic al or cognitive effects, glycaemic control, hormonal effects and later fertility.

The evidence cannot inform the safety of specific statins, doses or age at treatment initiation. It also cannot inform whether the risk-benefit balance of statins may differ according to baseline LDL-C/TC level or the criteria used to diagnose FH. A universal screening programme would identify children with FH who may otherwise have been detected clinically or through the cascade testing system. For these children, the benefits from starting statins are considered to outweigh any risks, even given the lack of longer term evidence. However, there is no evidence to inform whether diagnosing a young child with polygenic/multifactorial FH, and starting lifelong statin treatment on the basis of cholesterol level alone, could be associated with any harms.

No studies have assessed potential adverse effects from dietary or lifestyle approaches.

In summary, there is no evidence to inform whether a universal screening programme may be associated with harms. There is evidence that statins for children meeting diagnostic criteria for FH are safe in the short to medium term, up to 2.5 years. Even given the lack of longer term safety data, treatment is considered to be beneficial for this group. However, there is no evidence to inform whether the risk-benefit balance may

†† **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.

differ in children with multifactorial/polygenic FH. On the basis of these factors, this criterion is not met.

Review summary

Conclusions and implications for policy

The evidence to support a population-based universal child screening programme for FH is not currently available. As such, the findings do not indicate that a change to the current policy should be made and universal child FH screening should not be recommended.

Overall the volume, quality, applicability and direction of the evidence examined did not comprehensively answer the key questions:

1. There is remaining uncertainty over the optimal screening age (1–2 years or 9–10 years), test (TC and/or LDL-C) and test thresholds that would be used in a universal FH screening programme in children. One large prospective screening pilot of children aged 1–2 years found that half of children with FH variants had a TC level below the cut-off. Meanwhile almost a third did not have FH gene variants and were defined as having FH on the basis of having 2 sequential cholesterol samples above the threshold (multifactorial/polygenic FH). There is some uncertainty over the natural history of this condition and whether it is distinct from FH. Therefore there is need to understand how FH would be definitively diagnosed in the context of a universal screening programme, whether by the carriage of gene variants and/or positive family history indiciative of FH (as current diagnostic criteria), or by raised cholesterol alone, given this is the mediator of cardiovascular risk.
2. There is no evidence to inform whether universal screening affects FH-related morbidity or mortality compared with no screening. There is adequate evidence that statin treatment reduces LDL-C and TC levels at up to one year in children meeting diagnostic criteria for FH. Even given the lack of direct evidence that this reduces FH-related morbidity in the longer term, treatment is expected to be beneficial for this group. However, there is no evidence to inform whether starting lifelong statins is beneficial for children with multifactorial/polygenic FH diagnosed on the basis of cholesterol alone.
3. There is no evidence to inform whether or not a universal screening programme may be associated with any harms. There is evidence that statins for children meeting diagnostic criteria for FH are safe in the short to medium term up to the longest follow-up period (2.5 years). Even given the lack of longer term safety data, treatment is considered to be beneficial for this group. However, there is no evidence to inform whether the risk-benefit balance may differ in children with multifactorial/polygenic FH.

Further study may help to address these uncertainties:

1. Consensus on the diagnostic criteria that should be used to definitively diagnose FH in children identified through universal screening would be valuable. It may be helpful to better understand the genotype-phenotype relationship to see whether certain FH gene variants carry higher risk

of a child developing phenotypic FH and early atherosclerosis. Similarly, further study may help to understand whether the polygenic/multifactorial condition carries the same risk as monogenic FH or whether it should be considered a distinct condition. Understanding these aspects of the natural history of FH may help to inform the appropriate screening test when considering that a number of young children who carry FH variants may have lower cholesterol, while others may have raised cholesterol despite having no identified gene variant.

2. Long-term RCTs assessing whether universal screening (or treatment) of children with FH affects long-term cardiovascular morbidity and mortality may be neither ethical nor feasible. However, comparative studies would be useful to understand whether screening (or treatment) improves intermediate markers of atherosclerosis in the medium term, such as carotid intima-media thickness or endothelial function. It would also be beneficial to see whether this could differ by diagnostic criteria used for FH, age at treatment initiation, the statin or dose given.
3. Follow-up of universally screened populations would be helpful to see that the full screening programme is not associated with any harm, such as from over-diagnosis (e.g. children diagnosed with multifactorial/polygenic FH on the basis of elevated cholesterol alone, without confirmation through compatible family history/clinical signs), misclassification or missed diagnoses (e.g. those with monogenic FH who do not have raised cholesterol in young childhood) or psychological or quality of life effects.
4. Similarly further follow-up of treated children with FH is needed to see whether statins or other management approaches are safe in the longer term and do not have adverse effects on quality of life, liver and muscle function, neurological and cognitive development, diabetes, or growth and reproduction. Again it would helpful to see whether this may differ by diagnostic criteria used for FH, age at treatment, statin or dose given.
5. Future studies are needed to directly assess the views of the UK public and healthcare professionals towards universal screening for FH in young children; for example, whether there are any reservations towards early and lifelong treatment.

Limitations

The search strategy was built on a protocol developed *a priori* for each of the 3 key questions. Searching was limited to 3 literature databases and did not include grey literature resources. Studies only available in non-English language, editorials, abstracts, conference reports or poster presentations were not included. The reviewers were also unable to contact study authors or review non-published material. Background information on the ethics issues and potential controversy around universal screening was not based on a systematic search for evidence on this topic, and as such relevant literature or views may have been omitted.

Appendix 1 — Search strategy

Electronic databases

The search strategy included searches of the databases shown in Table 8: PubMed, the Cochrane Library (CDSR and CENTRAL) and Embase.

Table 8. Summary of electronic database searches and dates

Database	Platform	Searched on date	Date range of search
PubMed	PubMed.com	02 January 2019	1946 to search date
Embase	Embase.com	02 January 2019	1974 to search date
The Cochrane Library, including: - Cochrane Database of Systematic Reviews (CDSR) - Cochrane Central Register of Controlled Trials (CENTRAL)	Wiley Online	02 January 2019	CDSR: Issue 1 of 12, January 2019

Search Terms

Search terms included combinations of free text and subject headings, grouped into the following categories:

- disease area: familial hypercholesterolemia
- interventions: screening, diagnosis, treatment
- patient group: children

Search terms for Embase, PubMed, and the Cochrane Library are shown in Tables 9-11.

Table 9. Search strategy for Embase.com

Term Group	#	Search terms	Results
Interventions	1	'screening'/exp OR 'genetic screening'/mj	642,903
Interventions	2	screen*:ti,ab	914,469
Interventions	3	diagnos*:ti,ab	1,988,800
Interventions	4	detect*:ti,ab	2,680,643
Interventions	5	(genetic NEAR/2 test*):ti,ab	36,851
Interventions	6	#1 OR #2 OR #3 OR #4 OR #5	6,147,514
Disease area	7	'familial hypercholesterolemia'/mj	6,350
Disease area	8	((lipoprotein* NEAR/3 hyper*):ti,ab) AND 'type ii':ti,ab	53
Disease area	9	((hypercholesterol* OR hyperlipoprotein* OR cholesterol* OR lipoprotein*) NEAR/4 (familial OR essential)):ti,ab	10,737

Disease area	10	((cholesterol* OR lipoprotein*) NEAR/3 hyper*):ti,ab	8,756
Disease area	11	#7 OR #8 OR #9 OR #10	20,135
Population	12	'juvenile'/mj OR 'child'/exp	2,675,790
Population	13	child:ti,ab OR childhood:ti,ab OR children:ti,ab OR toddler:ti,ab OR infant:ti,ab OR juvenile:ti,ab	1,831,451
Population	14	#12 OR #13	3,207,114
	15	#6 AND #11 AND #14	1,038
Date/Languge/Pub type limit	16	#15 AND (2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py) AND [english]/lim NOT ([editorial]/lim OR [letter]/lim)	550
Database limit	17	#16 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)	317

Table 10. Search strategy for PubMed

Term Group	#	Search terms	Results
Disease area	1	"Hyperlipoproteinemia Type II"[Mesh]	6220
Disease area	2	familial hypercholesterol*[All fields]	6351
Disease area	3	familial hyperlipoprotein*[All fields]	154
Disease area	4	essential hypercholesterol*[All fields]	35
Disease area	5	essential hyperlipoprotein*[All fields]	362
Disease area	6	Hyper cholesterol*[All fields]	114
Disease area	7	hyper lipoprotein*[All fields]	17
Disease area	8	familial cholesterol*[All fields]	3
Disease area	9	essential cholesterol*[All fields]	7704
Disease area	10	Hyperlipoprotein* Type II[All fields]	6591
Disease area	11	lipoprotein* Type II[All fields]	5079
Disease area	12	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11)	18189
Intervention	13	"Mass Screening"[Mesh]	118747
Intervention	14	"Diagnosis"[Majr:NoExp]	13228
Intervention	15	"Early Diagnosis"[Majr:NoExp]	4764
Intervention	16	"Genetic Testing"[Mesh]	41658
Intervention	17	screen*[tiab]	668209
Intervention	18	diagnos*[tiab]	2277940
Intervention	19	detect*[tiab]	2132945
Intervention	20	genetic test*[tiab]	20939
Intervention	21	(#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20)	4529555
Population	22	("Child"[Mesh]) OR "Infant"[Mesh]	2340102

Population	23	(child[tiab] OR childhood[tiab] OR children[tiab] OR toddler[tiab] OR infant[tiab] OR juvenile[tiab])	1457732
Population	24	(#22 OR #23)	2741948
	25	(#12 AND #21 AND #24)	842
Language/Date limit	26	(#12 AND #21 AND #24) Filters: Publication date from 2008/01/01 to 2019/12/31; English	334

Table 11. Search strategy for the Cochrane Library Databases (Searched via the Wiley Online platform)

Term Group	#	Search terms	Results
Disease area	1	MeSH descriptor: [Hyperlipoproteinemia Type II] explode all trees	447
Disease area	2	((familial or essential) NEAR/4 (hypercholesterol* OR hyperlipoprotein* OR cholesterol*)):ti,ab	681
Disease area	3	hyper* NEAR/3 (cholesterol* OR lipoprotein*):ti,ab	844
Disease area	4	((lipoprotein* NEAR/3 hyper*):ti,ab) AND 'type ii':ti,ab	20
Disease area	5	(or #1-#4)	1633
Population	6	MeSH descriptor: [Child] explode all trees	1417
Population	7	MeSH descriptor: [Infant] explode all trees	15092
Population	8	(child OR childhood OR children OR toddler OR infant OR juvenile):ti,ab	96296
Population	9	(or #6-#8)	105191
Intervention	10	MeSH descriptor: [Mass Screening] this term only	2894
Intervention	11	MeSH descriptor: [Diagnosis] this term only	63
Intervention	12	MeSH descriptor: [Early Diagnosis] this term only	508
Intervention	13	MeSH descriptor: [Genetic Testing] explode all trees	427
Intervention	14	screen*:ti,ab	41866
Intervention	15	diagnos*:ti,ab	90426
Intervention	16	detect*:ti,ab	66592
Intervention	17	genetic near/2 test*:ti,ab	589
Intervention	18	(OR #10-#17)	174587
	19	#5 AND #9 AND #18	23

The 2017 Cochrane review[11] was considered to act as the baseline study for randomised controlled trials assessing the morbidity/mortality and adverse effects of statins in children with FH (questions 2 and 3). A top-up search was therefore conducted from January 2017 onwards in order to ensure that any later RCTs looking at the effects of statins in children with FH (diagnosed by any means) were identified. The top-up search is presented below:

Statins search terms 2017 onwards

Search terms included combinations of free text and subject headings, grouped into the following categories:

- interventions: statins
- patient group: children

Search terms for Embase, PubMed, and the Cochrane Library are shown in Tables 12-14.

Table 12. Search strategy for Embase.com

Term Group	#	Search terms	Results
Population	1	'juvenile'/mj OR 'child'/exp	2675790
Population	2	child:ti,ab OR childhood:ti,ab OR children:ti,ab OR toddler:ti,ab OR infant:ti,ab OR juvenile:ti,ab	1831451
Population	3	#1 OR #2	3207114
Intervention	4	'hydroxymethylglutaryl coenzyme a reductase inhibitor'/exp OR 'hydroxymethylglutaryl coenzyme a reductase inhibitor'	133716
Intervention	5	'ezetimibe'/exp OR 'ezetimibe'	9944
Intervention	6	statin*:ti,ab	62524
Intervention	7	atorvastatin:ti,ab OR fluvastatin:ti,ab OR pravastatin:ti,ab OR rosuvastatin:ti,ab OR simvastatin:ti,ab	31611
Intervention	8	lipistat:ti,ab OR zocor:ti,ab OR crestor:ti,ab OR lipitor:ti,ab OR lestor:ti,ab OR ezetrol:ti,ab	603
Intervention	9	((hydroxymethyl* OR 'hmg coa') NEAR/3 reductase) AND inhibitor:ti,ab	10266
Intervention	10	#4 OR #5 OR #6 OR #7 OR #8 OR #9	153546
	11	#3 AND #10	3986
Date/Language/Pub Type limit	12	#11 AND (2016:py OR 2017:py OR 2018:py) AND [english]/lim NOT ([editorial]/lim OR [letter]/lim)	925
Database limit	13	#12 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)	547

Table 13. Search strategy for PubMed

Term Group	#	Search terms	Results
Population	1	("Child"[Mesh]) OR "Infant"[Mesh]	2344476
Population	2	(child[tiab] OR childhood[tiab] OR children[tiab] OR toddler[tiab] OR infant[tiab] OR juvenile[tiab])	1461206
Population	3	(#1 OR #2)	2747411
Intervention	4	hydroxymethylglutaryl coa reductase inhibitors[MeSH Terms]	27406
Intervention	5	"ezetimibe"[MeSH Terms]	1901
Intervention	6	ezetimibe[All Fields]	3086
Intervention	7	statin*[All Fields]	39657
Intervention	8	(atorvastatin OR fluvastatin OR pravastatin OR rosuvastatin OR simvastatin OR HMG-COA)[All Fields]	23298
Intervention	9	((lipistat or zocor or crestor or lipitor or lestor or ezetrol))[All Fields]	20841
Intervention	10	(#4 OR #5 OR #6 OR #7 OR #8 OR #9)	58030
Intervention	11	(#3 AND #10)	1601
Date/Language limit	12	(#3 AND #10) Filters: Publication date from 2016/09/01 to 2019/12/31; English	246

Table 14. Search strategy for the Cochrane Library Databases (Searched via the Wiley Online platform)

Term Group	#	Search terms	Results
Population	1	MeSH descriptor: [Child] explode all trees	1417
Population	2	MeSH descriptor: [Infant] explode all trees	15092
Population	3	(child OR childhood OR children OR toddler OR infant OR juvenile):ti,ab	96296
Population	4	(or #1-#3)	105191
Intervention	5	MeSH descriptor: [Hydroxymethylglutaryl-CoA Reductase Inhibitors] explode all trees	3223
Intervention	6	MeSH descriptor: [Ezetimibe] explode all trees	610
Intervention	7	statin*:ti,ab	7026
Intervention	8	ezetimibe:ti,ab	1112

Intervention	9	(atorvastatin OR fluvastatin OR pravastatin OR rosuvastatin OR simvastatin):ti,ab	8623
Intervention	10	(lipistat or zocor or crestor or lipitor or lestor or ezetrol):ti,ab	141
Intervention	11	(hydroxymethyl* or HMG-COA) near/3 reductase inhibitor:ti,ab	765
Intervention	12	(OR #5-#11)	12612
	13	#4 AND #12	180

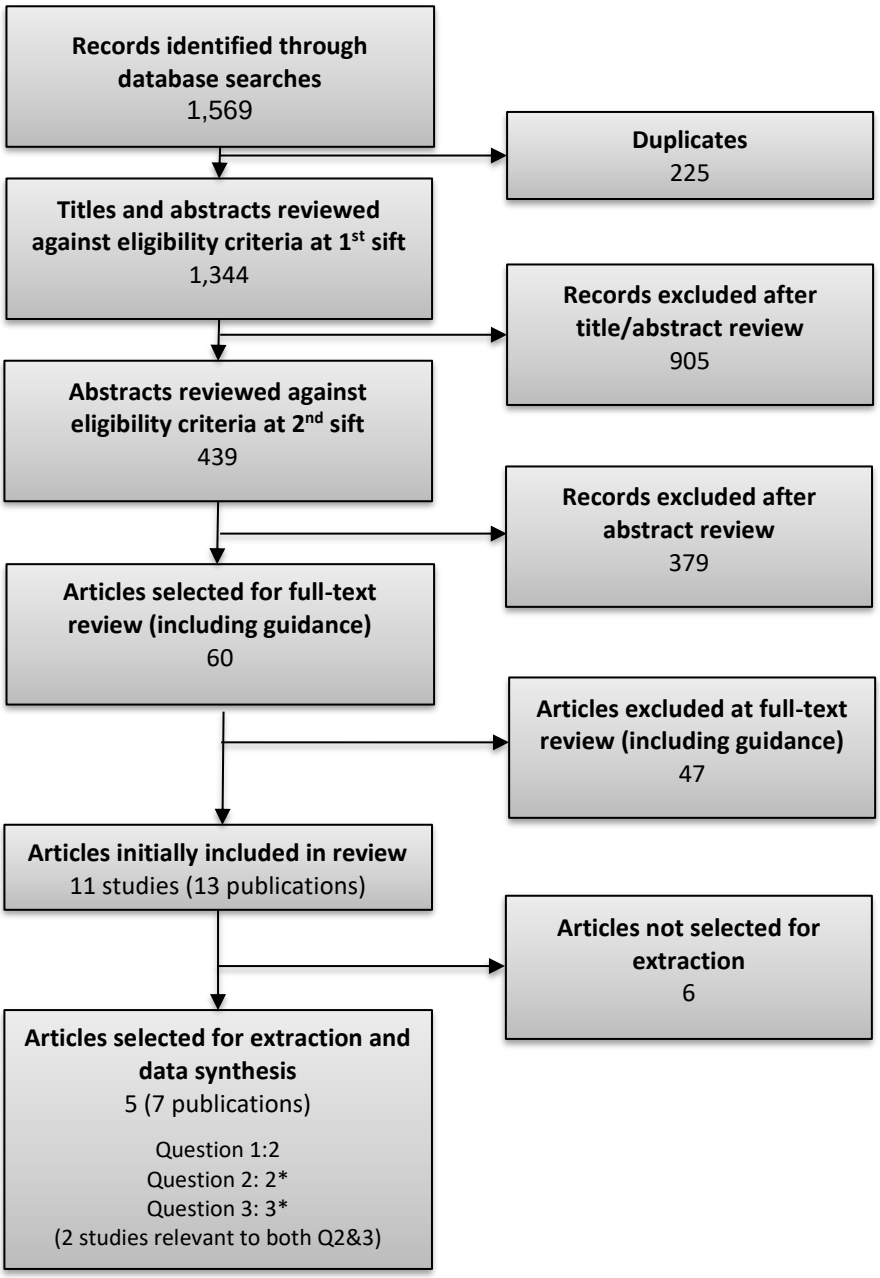
All results were imported into EndNote and de-duplicated.

Appendix 2 — Included and excluded studies

PRISMA flowchart

Figure 1 summarises the volume of publications included and excluded at each stage of the review. Four publications were ultimately judged to be relevant to one or more review questions and were considered for extraction. Publications that were included or excluded after the review of full-text articles are detailed below.

Figure 1. Summary of publications included and excluded at each stage of the review



Publications included after review of full-text articles

The 5 publications included after review of full-texts are summarised in Table 15 below. 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. Recent systematic reviews and meta-analyses of applicable study designs for each question would be considered the highest quality of evidence, if any were found. Following this, study designs would be prioritised for each question as listed in Table 2.
2. Studies relating to screening and treatment would be prioritised if they considered a UK population, followed by studies from Western populations analogous to the UK.

Publications not selected for extraction and data synthesis are clearly detailed in Table 16.

Table 15. Summary of publications included after review of full-text articles, and the question(s) each publication was identified as being relevant to

Study	The condition	The test	The intervention	The screening programme	Implementation criteria	Comments
Wald et al (2016)[9]	-	Q1	-	Q1	5	-
Futema et al (2017)[10]	-	Q1	-	Q1	5	-
USPSTF review (2016)[19, 23, 34]	-	-	-	Q2, Q3	11, 13	-
Vuorio et al (2017)[11]	-	-	Q2, Q3	-	11, 13	-
Humphries et al (2018)[12]	-	-	Q3	-	13	-

Publications excluded after review of full-text articles

60 publications were selected for full-text review. 11 studies were ultimately judged to have relevance to the key questions. The USPSTF review was covered by 3 documents giving 13 relevant publications. There were a further 10 documents of guidance or position statements. The remaining 37 publications that did not provide key evidence for the 3 key questions are listed in Table 16. However, note that some of these documents did provide information related to background context and potential ethical issues.

Table 16. Publications excluded after review of full-text articles

Reference	Reason for exclusion
Studies reviewed predominantly for potential relevance to KQ1 on test performance	
Cottrell L, John C, Murphy E, et al. Individual-, family-, community-, and policy-level impact of a school-based cardiovascular risk detection screening program for children in underserved, rural areas: the CARDIAC Project. J Obes. 2013;2013:732579.	The primary aim of project is to determine the prevalence of overweight/obese children and their associated comorbidities with secondary aim referral of those with chronic disease risk. Screening involved body composition and lipid profile. The study reports the characteristics of those identified and the number with suspected FH, but FH screening is not the primary aim neither does the study evaluate the accuracy of test cut-offs.
Groselj U, Kovac J, Sustar U, et al. Universal screening for familial hypercholesterolemia in children: The Slovenian model and literature review. Atherosclerosis. 2018;277:383-91.	Slovenian programme. Follow-up of n=280 screen positives (born 2007-2010): n=170 genotyped, reports how many had disease-causing variants in *LDLR* and *APOB* and gives sensitivity and specificity of 5, 6, 7 or 8 mmol/L cut-off with or without positive family history. Reportedly evaluated against the potential number of FH children from Slovinian registry of live births. Test accuracy is presumably based on assumed prevalence of FH (not specified). Excluded as this is not likely to give an accurate representation of test performance. No morbidity/mortality/harms data.
Ibarretxe D, Rodriguez-Borjabad C, Feliu A, et al. Detecting familial hypercholesterolemia earlier in life by actively searching for affected children:The DECOPIN project. Atherosclerosis. 2018;278:210-6.	Spain 2015-17, Tests two different pathways child-parent and parent child (cascade). Child-parent is not universal but opportunistic: primary care physicians asked to perform TC/LDL-C for any child needing a blood test for other clinical

	indication (n=13,039 TC and n=3540 full profile). Therefore excluded primarily as uncertain representation of the general child population. Additionally test performance cannot be determined: N=110 index children (based on cut-off and family history); DNA testing performed for their parents with Dutch Lipid Clinic Network score >8, and subsequently in children if this was positive. DNA sequencing was not performed in all screen positives, neither in screen negatives.
Klancar G, Groselj U, Kovac J, et al. Universal Screening for Familial Hypercholesterolemia in Children. J Am Coll Cardiol. 2015;66(11):1250-7.	Slovenian programme 1989-2009. Follow-up of n=272 screen positives: looks at how many had LDLR and APOB variants and other/multifactorial (not apparent any considered false negatives). Gives assumed sensitivity, based on estimated prevalence of FH overall either 1 in 200 or 1 in 500. Excluded as this is not likely to give an accurate representation of test performance. No morbidity/mortality/harms data.
Pang J, Martin AC, Bates TR, et al. Parent–child genetic testing for familial hypercholesterolaemia in an Australian context. Journal of Paediatrics and Child Health. 2018;54(7):741-7.	Cascade screening only form n=126 parents. Gives test performance of TC/LCL-C cut-offs to indicate presence of mutation but selective population of children at risk with an index parent.
Plana N, Rodriguez-Borjabad C, Ibarretxe D, et al. Lipid and lipoprotein parameters for detection of familial hypercholesterolemia in childhood. The DECOPIN Project. Clin Investig Arterioscler. 2018;30(4):170-8.	N=114 children identified through Spanish DECOPIN opportunistic child-parent and parent-child screening (known mutations and presumed polygenic) and n=110 controls (LDL-C below cut-off). Compares characteristics and gives AUC, sensitivity and specificity for cut-off to distinguish mutation carriers from non-carriers. No relevant data both in screening method (opportunistic and combining Ch-P and P-Ch populations), and in case-control design assuming all polygenic screen positives and controls (no DNA analysis) are true negatives for FH.
Wald DS, Wald NJ. Integration of child-parent screening and cascade testing for familial hypercholesterolaemia. J Med Screen. 2018:969141318796856.	Discusses hypothetical scenario of how may children and parents may be identified using parameters previously described in previous studies, e.g. screen 10,000 estimated to detect 40 children, 40 parents, 64 relatives. Presents the case for integrated child-parent-cascade screening but

	doesn't inform test performance, morbidity or harms questions.
Zawacki A, Dodge A, Eickhoff J, et al. Novel Lipid Thresholds for Screening Predict the Need for Pharmacotherapy. J Pediatr. 2018;202:220-5.e2.	Not looking at test accuracy for detection of FH. Retrospective cohort reviewing children presenting to US paediatric cardiovascular prevention clinics. Recorded TC/LDL-C levels and risk factors for cardiovascular disease including FH, but further testing not performed. Looks at test performance for different cut-offs for determining whether they met recommended criteria for prescription of statins.
Screening studies reviewed predominantly for potential content related to KQ 2and 3 on screening harms or mortality/morbidity effects	
Bamba V. Update on screening, etiology, and treatment of dyslipidemia in children. J Clin Endocrinol Metab. 2014;99(9):3093-102.	Review of the NHLBI recommendations and additional evidence review of publications related to screening and prevention of dyslipidaemia and atherosclerosis. Provides contextual information around ethics and potential controversy but does not provide evidence for the morbidity/mortality or harms questions.
Benuck I. Point: The rationale for universal lipid screening and treatment in children. J Clin Lipidol. 2015;9(5 Suppl):S93-s100.	Narrative predominantly presenting NHLBI recommendations and the case for universal screening. No relevant evidence for morbidity/mortality or harms questions.
de Ferranti SD, Rodday AM, Parsons SK, et al. Cholesterol Screening and Treatment Practices and Preferences: a Survey of United States Pediatricians. Journal of Pediatrics.2017;185:99-105.	Survey of 700 US physicians on screening views in light of varied NHLBI recommendations to screen all 9-11 year olds, including views on prescribing statins - though not specific to views on universal screening for FH. Some relevance to general views and ethical issues but doesn't provide evidence for KQ3 on screening harms.
Dixon DB, Kornblum AP, Steffen LM et al. Implementation of lipid screening guidelines in children by primary care providers. J Pediatr. 2014;164(3):572-6.	500 US physicians questioned on screening practice and views on universal screening. Includes mention of barriers such as uneasiness in addressing lipid disorders in children – though not specific to views on universal screening for FH. Some relevance to general views and ethical issues but doesn't provide evidence for KQ3 on screening harms.
Keenan KF, Finnie RM, Simpson WG, et al. Parents' views of genetic testing and treatment of familial hypercholesterolemia in children: a qualitative study. Journal of Community Genetics. 2018:1-13.	Qualitative study representing the views of 17 parents with FH and their experience of genetic testing and statin treatment in children. Discusses positive and negative views with some relevance to general views and ethical issues, but as this relates to cascade screening it can't be applied to

	universal. Doesn't meet inclusion criteria for KQ3 on screening harms.
King K, Macken A, Blake O, et al. Cholesterol screening and statin use in children: a literature review. Irish Journal of Medical Science. 2018:1-10.	Broad literature search into hypercholesterolaemia and the use of statins. Discussion primarily relates to NHLBI recommendations. Mentions potential issues around screening without citation to specific studies, in addition to the Dixon et al survey of practitioner views. Some relevance to general views and ethical issues but doesn't provide evidence for KQ3 on screening harms.
Kusters DM, Avis HJ, de Groot E, et al. Ten-year follow-up after initiation of statin therapy in children with familial hypercholesterolemia. Jama. 2014;312(10):1055-7.	Letter only.
Kusters DM, de Beaufort C, Widhalm K, et al. Paediatric screening for hypercholesterolaemia in Europe. Arch Dis Child. 2012;97(3):272-6.	Provides an overview of different screening practices in the US and Europe. Has a section on potentially harmful aspects of screening but it is not a systematic review. Cites pre-2008 studies. Provides some background information to general views and ethical issues but does not provide evidence for KQ3 on screening harms.
Kwiterovich PO, Gidding SS. Universal screening of cholesterol in children. Clin Cardiol. 2012;35(11):662-4.	Narrative discussion around universal screening, mentions concerns about labelling a child as having high cholesterol but states there is no data in that regard.
Martin AC, Bell DA, Brett T, et al. Beyond cascade screening: detection of familial hypercholesterolaemia at childhood immunization and other strategies. Curr Opin Lipidol. 2017;28(4):321-7.	Narrative around potential screening strategies, including child-parent as studied by Wald et al but does not cover relevant information for test, morbidity/mortality or harms questions.
McCrindle BW. Familial hypercholesterolemia in children and adolescents. Curr Opin Lipidol. 2012;23(6):525-31.	Narrative around NHLBI recommendations. Mentions concerns around screening but it is not a systematic search and citations are to editorials/commentaries only. Some background to general views and ethical issues but doesn't provide evidence for KQ3 on screening harms.
Meulenkamp TM, Tibben A, Mollema ED, et al. Predictive genetic testing for cardiovascular diseases: impact on carrier children. Am J Med Genet A. 2008;146a(24):3136-46.	Netherlands, 16 children with FH discuss understanding of the condition and whether they have any concerns. Similarly relevant to general discussion but as this relates to cascade screening it can't be applied to universal. Doesn't meet inclusion criteria for KQ3 on screening harms.

Smith AJ, Turner EL, Kinra S. Universal Cholesterol Screening in Childhood: A Systematic Review. Acad Pediatr. 2016;16(8):716-25.	Systematic review of studies evaluating effects of screening on health outcomes (finding no studies). Search date Jan 2016 prior to USPTF search on morbidity/mortality outcomes. Also covers acceptability and views relevant to general discussion around ethics and acceptability but not covering harms.
Wald DS, Kasturiratne A, Godoy A, et al. Child-parent screening for familial hypercholesterolemia. J Pediatr. 2011;159(5):865-7.	Pilot study included in the last UK NSC review. All practitioners and 98% of parents found screening acceptable. Relevant to general discussion around ethics and acceptability but doesn't provide information on screening harms.
Weiner K, Durrington PN. Patients' understandings and experiences of familial hypercholesterolemia. Community Genet. 2008;11(5):273-82.	UK interviews with 31 adults with FH with mixed views, around half saying they'd have their child tested and others concerned about medicalising at a young age. Relevant to general discussion but as this relates to cascade screening it can't be applied to universal. Doesn't meet inclusion criteria for KQ3 on screening harms.
Wilson DP, Davis S, Matches S, et al. Universal cholesterol screening of children in community-based ambulatory pediatric clinics. J Clin Lipidol. 2015;9(5 Suppl):S88-92.	No relevant content to test accuracy, morbidity/mortality or harms. Compares screening practices at clinics before and after NHLBI recommendations to screen all children aged 9-11 years.
Zachariah JP, McNeal CJ, Copeland LA, et al. Temporal trends in lipid screening and therapy among youth from 2002 to 2012. J Clin Lipidol. 2015;9(5 Suppl):S77-87.	Rates of lipid testing across 5 US health systems 2002-12 and change in response to recommendations. Mentions controversy, but not systematic search and again citation of editorials/commentaries. Doesn't provide evidence for KQ3 on screening harms.
Studies reviewed for potential relevance to treatment-related morbidity/mortality effects or harms	
Braamskamp M, Langslet G, McCrindle BW, et al. Effect of Rosuvastatin on Carotid Intima-Media Thickness in Children With Heterozygous Familial Hypercholesterolemia: The CHARON Study (Hypercholesterolemia in Children and Adolescents Taking Rosuvastatin Open Label). Circulation. 2017;136(4):359-66.	Assesses the effect of statins on CIT in children with FH compared to unaffected siblings; concludes early treatment is beneficial because it gets them to normal; but no comparison to those with FH untreated
Dale P, Shortland GJ, Datta D, et al. Hyperlipidaemia in paediatric practice. Paediatrics and Child Health (United Kingdom). 2015;25(3):149-53.	General discussion of UK practice. No content related to harms of screening.

Desai NK, Mendelson MM, Baker A, et al. Hepatotoxicity of Statins as determined by Serum Alanine Aminotransferase in a Pediatric Cohort with Dyslipidemia. J Pediatr Gastroenterol Nutr. 2018.	N=2704 in US registry with liver function measured 2010-14. Compares measures in users and non-users of statins, and before/after in statin users. Various cardiovascular risk factors are listed among participant characteristics (e.g. BMI, diabetes, family history CVD) but no mention of FH specifically. Therefore excluded on uncertain population applicability.
Harada-Shiba M, Kastelein JJP, Hovingh GK, et al. Efficacy and Safety of Pitavastatin in Children and Adolescents with Familial Hypercholesterolemia in Japan and Europe. Journal of atherosclerosis and thrombosis. 2018;25(5):422-9.	Post-2017 Cochrane search for statins in HeFH. Excluded on design. Reporting the effects of a dose-comparison study in n=14 Japanese adolescents with the effect seen in the Braamskamp 2015 trial included by the Cochrane review.
Hennig M, Brandt A, Bautembach-Minkowska J, et al. When do paediatric patients with familial hypercholesterolemia need statin therapy? Dev Period Med. 2017;21(1):43-50.	Post-2017 Cochrane search for statins in HeFH. Non-comparative cohort (n=57) all treated by diet with or without the addition of statins. Looks at the effect on cholesterol levels by age. Not applicable to treatment effects as non-comparative and no information on adverse effects.
Johnson PK, Mendelson MM, Baker A, et al. Statin-Associated Myopathy in a Pediatric Preventive Cardiology Practice. J Pediatr. 2017;185:94-8.e1.	N=474 in US registry with creatinine kinase measured 2010-14. Compares measures in users and non-users of statins, and before/after in statin users. Various cardiovascular risk factors are listed among participant characteristics. Lists family history of hypercholesterolemia for n=222; presumably this is FH but unclear, and no separate analysis for this population. Therefore excluded on uncertain population applicability.
Joyce NR, Zachariah JP, Eaton CB, et al. Statin Use and the Risk of Type 2 Diabetes Mellitus in Children and Adolescents. Acad Pediatr. 2017;17(5):515-22.	Matches n=2,085 statin users with non-users in US medical database 2003-14. Compares risk of type 2 diabetes in those with and without dyslipidaemia, finding risk is increased only among those without dyslipidaemia. Reports performing sensitivity analysis for 'patients with the ICD-9 code 272.0 for "pure hypercholesterolemia", which includes heFH' but the analyses are not certainly specific to those with FH. Therefore excluded on uncertain population applicability.
Makino H, Tamanaha T, Harada-Shiba M. LDL apheresis in Japan. Transfus Apher Sci. 2017;56(5):677-81.	Uncertain content from abstract. Non-systematic review reporting a couple of small case series of lipoprotein apheresis for HoFH.

Radaelli G, Sausen G, Cesa CC, et al. Statin treatments and dosages in children with familial hypercholesterolemia: Meta-analysis. Arquivos Brasileiros de Cardiologia. 2018;111(6):810-21.	Systematic review of statin use with search date Feb 2016. Cochrane selected in preference which post-dates this.
Ramaswami U, Cooper J, Humphries SE. The UK Paediatric Familial Hypercholesterolaemia Register: preliminary data. Arch Dis Child. 2017;102(3):255-60.	Preliminary data from the UK Paediatric FH Registry (n=200). Reports effects on liver function and creatinine kinase, but these outcomes are covered in later 2018 registry report by Humphries et al including n=300. Reports change in LDL-C levels in treated and non-treated children, but baseline characteristics and cholesterol levels are different.
Stock J. Landmark position paper on paediatric familial hypercholesterolaemia from the EAS Consensus Panel. Atherosclerosis. 2015;242(1):277-80.	Discussion of the EAS statement. Contextual information but does not provide evidence for the morbidity/mortality or harms questions.
Vuorio A, Kovanen PT. Decreasing the cholesterol burden in heterozygous familial hypercholesterolemia children by dietary plant stanol esters. Nutrients. 2018;10(12).	Narrative review discussing the general understanding around plant esters as dietary treatment for FH. Cites small non-RCTs.

Appendix 3 — Summary and appraisal of individual studies

Data Extraction

Table 17. Studies relevant to Criterion 5

Study reference	Study design	Population characteristics	Index test	Reference standard	Accuracy

Wald et al 2016[9]	Prospective screening cohort, UK
	
	Child immunisation programme, 92 general practices, March 2012 to 2015.
		n=10,095 children (median age 12.7 months, 52% male)
		
		Representative of n=13,097 invited to participate; n=11,010 (84%) agreed participation; satisfactory sample obtained for n=10,118 (8% sampling failure rate); with n=23 incorrect transcription results (<0.3% failure rate).
			TC ≥1.53 multiples of the median (MoM) of all children screened.
			
			Initially the pilot study[32] was used to inform MoM which was updated after n=2000 screened.
				FH48 panel of variants.
				
				Including 46 most common *LDLR* variants in the Regional Genetics laboratory, and one *APOB* and *PCSK9* variant.
				
				Children with TC ≥1.53 but no FH48 variant received full DNA sequencing of the 3 genes.
				
				Those with no variant had repeat TC at 3 months
				
				FH diagnosis (true positive):
				• TC ≥1.53 plus identified variant
				• 2 x TC ≥1.53
				
				The programme was child-parent incorporating reverse cascade testing of parents. Results for this are not reported here.
					92 screen positive (TC ≥1.53 MoM):
					• 13 with FH48 variant
					• 7 with variant on DNA sequencing
					• 72 with no variant on DNA sequencing:
					  ○ 8 with repeat TC ≥1.53 MoM
					  ○ 64 with repeat TC <1.53 MoM
					
					= 28 true positive, 64 false positive
					
					10,003 screen negative (TC <1.53 MoM):
					• 17 with FH48 variant
					• 9,986 with no FH48 variant
					• (no further DNA testing)
					
					=17 false negatives using FH48 panel only.
					False and true negatives can't be known with certainty; the proportion who would have TC<1.53 and a variant on DNA testing is unknown.
					
					Test accuracy for presence of FH48 variant

<table>
<tr><th>Study reference</th><th>Study design</th><th>Population characteristics</th><th>Index test</th><th>Reference standard</th><th>Accuracy</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>
<table>
<tr><td></td><td>FH48</td><td>No FH48</td></tr>
<tr><td>+ve test</td><td>13</td><td>79</td></tr>
<tr><td>-ve test</td><td>17</td><td>9986</td></tr>
</table>
PPV=13/92=14.1%
NPV=9986/10003=99.8%
Sensitivity=13/30=43.3%
Specificity=9986/10065=99.2%
FPR=0.8%

Test accuracy for presence of FH48 variant or variant on DNA testing
<table>
<tr><td></td><td>FH variant</td><td>No variant</td></tr>
<tr><td>+ve test</td><td>20</td><td>72</td></tr>
<tr><td>-ve test</td><td>17*</td><td>9986*</td></tr>
</table>
PPV=20/92=21.7%
NPV=9986/10003=99.8%*
Sensitivity=20/37=54.0%*
Specificity=9986/10058=99.3%*
FPR=0.7%*

* can’t be known with certainty due to potential verification bias.

Allowing for limited sequencing, the authors estimate a lower sensitivity of 47% at the same specificity and FPR.

Test accuracy for FH diagnosis (variant on FH48 panel or DNA sequence; or 2 raised TC)
<table>
<tr><td></td><td>FH</td><td>No FH</td></tr>
<tr><td>+ve test</td><td>28</td><td>64</td></tr>
<tr><td>-ve test</td><td>17*</td><td>9986*</td></tr>
</table>
</td></tr>
</table>

Study reference	Study design	Population characteristics	Index test	Reference standard	Accuracy
					PPV=28/92=30.4% NPV=9986/10003=99.8%* Sensitivity=28/45=62.2%* Specificity=9986/10050=99.4%* FPR=0.6%* * can't be known with certainty due to potential verification bias. Allowing for limited sequencing, the authors estimate a lower sensitivity 55% with the same Sp and FPR *Parental testing* - 32/37 parents of children with an FH variant received testing (5 declined/were unavailable) - 25/28 parents with positive test results (assumed to be presence of variant) subsequently started statins (none on prior treatment) - States that no parents reported negative effects and said screening was worthwhile – however, there is no further exploration of this. It's unclear whether this relates to their own diagnosis and treatment or future care and management of the child. - 16% declined participation in the screening study and reasons for this were not explored The authors then apply a hypothetical scenario of screening 10,000 children and lowering the TC cut-off to ≥1.35

Study reference	Study design	Population characteristics	Index test	Reference standard	Accuracy

					MoM with 'reflex' DNA testing on the same blood sample
					Test positive would therefore be:
					- TC ≥1.35 MoM plus FH variant; or
					- 1st and repeat TC≥1.50 MoM
					
					This was expected to identify an additional 12/10,000 children but needs validation:
					
					10,000 children screened:
					- 500 have TC ≥1.35
					- 32 children have FH variant on full DNA sequencing)
					- 468 children with no FH variant
					  ○ 80 with TC ≥1.50 MoM have repeat
					  ○ 8 have repeat TC ≥1.50 MoM
					- 40 children identified per 10,000: case rate of 4 per 1000

Futema et al 2017[10]	Retrospective cohort, UK Avon Longitudinal study of Parents and Children (ALSPAC) cohort who had blood samples taken at 9 years.	n=5,083 children (mean age 9.9 years) with blood samples taken n=1,503 screen negatives randomly selected for low-read depth whole genome sequencing (successful in n=1,497, 29.5%) n=55 screen negatives (4%) randomly selected for targeted high-read sequencing (stratified by LDL-C)	TC >1.53 MoM LDL-C >1.84 MoM As informed by the 2007 Wald et al SR of case control studies[8]	Low-read depth whole genome sequencing of screen negatives with random sample n=55 received targeted high-read sequencing of *LDLR, APOB* and *PCSK9* All n=15 screen positives received targeted high-read sequencing.	From n=1,512 receiving DNA sequencing, an FH variant was identified in n=6 (4 with LDLR and 2 with an APOB variant) **TC >1.53 MoM** Median TC was 4.23mmol/L giving a threshold value of 6.47mmol/L for 1.53 MoM (at estimated FPR 0.1%) • 2/6 true positives (TC >1.53 MoM) had an FH variant • 4/6 false negatives (TC <1.53 MoM) had a variant

<table>
<tr><th>Study reference</th><th>Study design</th><th>Population characteristics</th><th>Index test</th><th>Reference standard</th><th>Accuracy</th></tr>
<tr><td></td><td></td><td>all n=15 screen positives with LDL-C >1.84 MoM and TC >1.53 MoM all received targeted high-read sequencing</td><td></td><td></td><td>Test accuracy for presence of FH variant
<table><tr><td></td><td>FH</td><td>No FH</td></tr><tr><td>+ve test</td><td>2</td><td>13</td></tr><tr><td>-ve test</td><td>4</td><td>1493</td></tr></table>
Reported test accuracy:
Sensitivity: 2/6=33%
Specificity=99.1%
FPR=0.9%
PPV=13/15=13.3% NB study table reports 12.5%
NPV=1493/1497=99.7%
Extrapolating to the full cohort of n=5,083 gave the same parameters at lower FPR 0.3% (Sp 99.7%)
With further correction for verification bias (only random sample of screen negatives having high-depth targeted sequencing):
Sensitivity: 25%
Specificity=99.6%
FPR=0.4%
PPV=9.1%
NPV=99.9%
With additional correction for misclassification based on reduced sensitivity (90%) of high-depth targeted sequencing gives sensitivity:</td></tr>
</table>

<table>
<tr><th>Study reference</th><th>Study design</th><th>Population characteristics</th><th>Index test</th><th>Reference standard</th><th>Accuracy</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>22.2% with other performance measures the same.

LDL-C >1.84 MoM

Median LDL-C in the full sample was 2.3mmol/L giving a threshold value of 4.25mmol/L for 1.84 MoM (at estimated FPR 0.1%)

• 5/6 true positives (LDL-C >1.84 MoM) had an FH variant

• 1/6 false negatives (LDL-C <1.84 MoM) had a variant

Test accuracy for presence of FH variant
<table><tr><td></td><td>FH</td><td>No FH</td></tr><tr><td>+ve test</td><td>5</td><td>12</td></tr><tr><td>-ve test</td><td>1</td><td>1494</td></tr></table>
Reported test accuracy:

• Sensitivity: 5/6=83%

• Specificity: 1494/1506=99.2%

• FPR=0.8%

• PPV: 5/17=29.4%

• NPV: 1494/1495=99.9%

Extrapolating to the full cohort of n=5,083 gave the same parameters at lower FPR 0.2% (Sp 99.8%)

With further correction for verification bias:</td></tr>
</table>

Study reference	Study design	Population characteristics	Index test	Reference standard	Accuracy
					• Sensitivity=62.5% • Specificity=99.8% • FPR=0.2% • PPV=29.4% • NPV=99.9% With additional correction for misclassification based on reduced sensitivity of high-depth targeted sequencing: sensitivity 66.7% and PPV 35.3% with other performance measures reported the same. Further hypothetical analysis of 10,000 screened using LDL-C is given, based on assumed prevalence of 1 in 500 and adjusting for verification bias and misclassification (not reported here).

Table 18. Systematic reviews relevant to Criteria 11 and 13

Study reference	Study design and objective	Data sources and search dates	Study inclusion criteria	Included studies	Outcomes
USPSTF evidence review 2016[19, 23, 34]	Systematic review of the benefits and harms of screening children and adolescents for HeFH. Structured around 4 key	AHRQ, BMJ Clinical Evidence, Canadian Agency for Drugs and Technologies in Health, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment (Centre for Reviews and Dissemination), Institute for	For screening questions 1-4 (relevant to this review): studies of asymptomatic children and adolescents aged 0-20 years at the time of screening. Acceptable screening interventions were defined as a lipid panel (fasting or non-fasting TC or LDL-C	Question 1 and 2 on screening effects on FH-related morbidity or intermediate outcomes: No studies identified. Question 4 on harms of screening: No studies identified.	NA

Study reference	Study design and objective	Data sources and search dates	Study inclusion criteria	Included studies	Outcomes
	questions related to screening and 4 questions related to treatment. Note, only questions 1, 2 and 4 were relevant to this evidence review. **Screening** 1. Does screening for FH in asymptomatic children and adolescents delay or reduce the incidence of MI or stroke in adulthood? a. Selective screening based on family history b. Universal screening 2. Does screening for FH in asymptomatic children and adolescents	Clinical Systems Improvement, Institute of Medicine, MEDLINE and PubMed, and National Institute for Health and Care Excellence. Initial search September 2005 (date of the last review) to October 2013. Update searches June 2014 and June 2015. Ongoing surveillance through targeted search of high-impact journals and article alters up to April 2016. All studies included in the last USPSTF review were also included.	alone or in combination with HDL-C) delivered in a universal or selective screening strategy. Exclusions: screening studies that focused on genetic screening alone or cascade screening; screening studies of populations with known dyslipidemia, a diagnosis associated with secondary dyslipidemia, or a documented family history of FH; screening studies that did not report the number of children with probable or definite FH.		

Study reference	Study design and objective	Data sources and search dates	Study inclusion criteria	Included studies	Outcomes
	improve intermediate outcomes (i.e. reduce lipid concentrations or reverse or slow the progression of atherosclerosis) in childhood and adolescence? a. Selective screening based on family history b. Universal screening 3. What is the diagnostic yield of appropriate screening tests for FH in children and adolescents? a. Selective screening based on family history b. Universal				

Study reference	Study design and objective	Data sources and search dates	Study inclusion criteria	Included studies	Outcomes
	screening 4. What are the harms of screening for FH in children and adolescents? **Treatment** 5. Does treatment of FH with lifestyle modifications and/or lipid-lowering medications in children and adolescents delay or reduce the incidence of adult MI and stroke events? 6. Does treatment of FH with lifestyle modifications and/or lipid-lowering medications in children and adolescents improve intermediate outcomes (i.e. reduce lipid concentrations or reverse or slow				

Study reference	Study design and objective	Data sources and search dates	Study inclusion criteria	Included studies	Outcomes
	the progression of atherosclerosis) in childhood and adolescence? 7. What are the harms of treatment of FH with medications in children and adolescents? 8. What is the association between intermediate outcomes in childhood and adolescence and future incidence or timing of adult MI and stroke events? In these questions intermediate outcomes included lipid concentrations (TC and LDL-C) and atherosclerosis markers (carotid intima thickness, calcium score, and pathological findings).				

Study reference	Study design and objective	Data sources and search dates	Study inclusion criteria	Included studies	Outcomes
Vuorio et al 2017[11]	Systematic review to assess the effectiveness and safety of statins in children with HeFH.	Relevant studies were identified from the Group's Inborn Errors of Metabolism Trials Register using terms related to Hypercholesterolemia AND Statin. The Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated with each new issue of the Cochrane Library), weekly searches of MEDLINE and the prospective hand-searching of the Journal of Inherited Metabolic Disease. Unpublished work was identified by searching through the abstract books of the Society for the Study of Inborn Errors of Metabolism conference and the SHS Inborn Error Review Series. The search was supplemented by searching the references of retrieved reviews and primary research. No restrictions to language or publication status. Date of most recent search: 20 February 2017.	RCTs and non-randomised controlled studies in children and adolescents aged ≤18 years (at study start) with clinical diagnosis of HeFH based on genetic testing or clinical criteria, and comparing a statin with placebo, alternative statin, other lipid-lowering therapy or diet alone. Outcomes of interest **Primary outcomes** 1. Change in carotid intima-media thickness (CIMT) 2. Change in serum LDL-C 3. Change in measures of growth and maturation, e.g. age of onset of puberty **Secondary outcomes** 1. Liver dysfunction: change in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels (>3x upper limit of normal) 2. Myopathy: change in serum creatinine kinase (CK) level (>10x upper limit of normal) 3. Rhabdomyolysis (degeneration of skeletal	9 RCTs (n=1,177) published from 1996 to 2015. 6 RCTs were international/multicentre, 3 were single centre. All were representative of western populations. 6 studies included >100 children (one with >100 per treatment arm). The intervention and follow-up periods ranged from 6 weeks to 24 months, with a median 24 weeks. **Included population** Variable age range: 3 studies 10-17 and one study each of 6-17, 8-16, 8-17, 8-18, 11-17 and 11-18. All studies defined inclusion by LDL-C level in addition to: 6 studies required family history of FH, one study a genetic diagnosis in the child, one either genetic or clinical criteria and one study outlined genetic criteria or family history of early cardiovascular disease. <u>Interventions</u> 2 studies used lovastatin (40mg daily), one study pravastatin (5-20mg daily), one pravastatin (20-40mg),	**Morbidity-related effects** Change in LDL-C: Moderate quality evidence that statins reduce LDL-C vs placebo at up to 48 weeks follow-up: mean difference -32.15% (95% CI -29.40 to -34.90%) (6 studies, n=669; I^2 =89%) By follow-up time: • One month (3 studies, n=228): mean difference [MD] -24.59% (95% CI -30.11 to -19.08) • 6 months (4 studies, n=528): MD -34.97% (95% CI -37.51 to -32.44) • One year (2 studies, n=254): MD -26.94% (95% CI -31.64 to -22.23) Heterogeneity across all analyses. Change in TC: Statins reduce TC vs placebo at up to one year follow-up: MD -26.53% (95% CI -28.54 to -24.51%) (6 studies, n=669) By follow-up time: • One month (3 studies, n=228): MD -18.31 (95% CI -22.55 to -14.06) • 6 months (4 studies, n=528): MD -24.28 (95% CI -26.09 to -22.47) • One year (2 studies, n=254): MD -27.60 (95% CI -30.64 to -24.57) Heterogeneity at 6 month and one year analyses. Triglyceride: no change at up to one year (MD -3.27%, 95% CI -12.03 to +5.50%) (5 studies, n=525) HDL-C: statins increased levels at up to one year (MD +3.11%, 95% CI +0.55 to +5.67%) (6 studies, n=669)

Study reference	Study design and objective	Data sources and search dates	Study inclusion criteria	Included studies	Outcomes
			muscle tissue) or death due to rhabdomyolysis 4. Change in endothelial function (measured by flow-mediated dilation of the brachial artery) 5. Change in serum TC, HDL-C and triglyceride (TG) 6. Quality of life 7. Compliance to study medication 8. Other adverse events that may be associated with statins	one simvastatin (20mg daily), one simvastatin (40mg daily), one atorvastatin (10-20mg daily), one rosuvastatin (5-20mg daily) and one pitavastatin (1-4mg daily). <u>Morbidity-related effects</u> All 9 studies assessed change in LDL-C and it was the primary outcome in 8 studies. Change in CIMT was the primary outcome of one study. <u>Harms</u> 8 studies reported AST or ALT change, 7 studies reported CK changed. 3 studies reported effects on puberty, 4 reported effects on steroid and sex hormones. 6 studies reported adverse effects. <u>Risk of bias</u> There was low risk of bias related to blinding and low rate of drop-out across all studies. All studies had uncertain risk of bias related to method of randomisation and allocation concealment (selection bias) and uncertain risk of selective reporting bias.	Change in CIMT: Low quality evidence that statins reduce CIMT vs placebo at 24 months: MD -0.01mm, 95% CI -0.03 to -0.00 (1 study, n=211) Change in endothelial function: Low quality evidence that statins improve endothelial function at up to one year: absolute change 2.70% higher (95% CI 0.42 to 4.98%) vs 1.2% change (95% CI not reported) in the placebo group (1 study, n=50) <u>Harms</u> Growth and maturation: Low quality evidence that statins have no effect vs placebo on the proportion with Tanner puberty stage ≥1 at up to 2 years: • At 6 months (2 studies, n=355): risk ratio (RR) 0.99 (95% CI 0.66 to 1.50) • One year (one study, n=139): RR 0.89 (95% CI 0.51 to 1.54) • 2 years (1 study, n=211): RR 0.95 (95% CI 0.77 to 1.18) Liver dysfunction: Low quality evidence that statins had no effect on AST or ALT at up to 2 years follow-up: • One month (2 studies, n=175): AST and ALT (RR 0.00, 95% CI 0.00 to 0.00) • 6 months (4 studies, n=538): AST (RR 2.40, 95% CI 0.29 to 19.85) and ALT (RR 2.03, 95% CI 0.24 to 16.95) • One year (2 studies, n=254): AST and ALT (RR 2.03, 95% CI 0.08 to 49.09)

Study reference	Study design and objective	Data sources and search dates	Study inclusion criteria	Included studies	Outcomes
					• 2 years (1 study, n=211): AST (RR 0.21, 95% CI 0.01 to 4.23) and ALT (RR 0.00, 95% CI 0.00 to 0.00) Overall across all studies there were 4 cases of changed AST and 4 of changed ALT in the statins group vs 2 cases of AST change and 0 cases of ALT change in the placebo group (no cases at one month) (total 7 studies, n=924). Myopathy: Low quality evidence that statins had no effect on CK at up to one year follow-up: • One month (3 studies, n=330): RR 3.23 (95% CI 0.18 to 58.84) • 6 months (2 studies, n=229): RR 0.22 (95% CI 0.01 to 5.28) • One year (2 studies, n=254): RR 0.67 (95% CI 0.04 to 10.57) Overall 5 cases of CK change in the statin group vs 2 cases in the placebo group at all time points (total 6 studies, n=669). Adverse effects: Moderate quality evidence that statins did not increase adverse effects at up to one year follow-up: total 402/1000 events vs 399/1000 placebo (RR 1.01, 95% CI 0.81 to 1.26) (2 studies, n=276). Also no effect at: • One month (2 studies, n=248): RR 0.86 (95% CI 0.65 to 1.13) • 6 months (3 studies, n=416): RR 1.02 (95% CI 0.82 to 1.27) Adverse effects were variably defined and not standardised across studies; no further detail is provided. No evidence on quality of life.

Study reference	Study design and objective	Data sources and search dates	Study inclusion criteria	Included studies	Outcomes
					Compliance: one study reports 84% of tablets taken (no further detail)

Table 19. Cohort study relevant to Criterion 13

Study reference	Study design and objective	Population	Treatment	Outcomes
Humphries et al (2018)[12]	Use of the UK Paediatric FH register to determine: 1. the prevalence of plasma markers of liver toxicity and muscle damage in statin-treated children with FH 2. to compare growth rates in statin-treated and non-treated children with FH 3. to review the prevalence of obesity in FH children compared to the UK general population (not further reported here) The register was established in 2012. All lipid clinics in the UK were contacted electronically and a web-based data capture tool collected information on patient characteristics and clinical details. Clinicians are sent	N=300 children with HeFH: n=135 (45%) treated with statins vs n=165 untreated 51% male, 75% white ethnicity, untreated LDL-C 5.5mmol/L Characteristics that were significantly different between statin users vs non-users (p≤0.05): • Age (mean 10.7 vs 9.5 years). Proportion of cohort treated by age group: ○ 0-5 years: none ○ 5-10 years: 16.7% ○ 10-15 years: 57.1% ○ >15 years: 73.2% • Family history of heart disease (43.7% vs 32.7%) • TC (mean 7.79 vs 7.15mmol/l)	Of n=135 prescribed statins, n=128 were still on statins at follow-up. Statin use reported for n=128: atorvastatin (49.2%, n=63), pravastatin (27.3%, n=35), simvastatin (21.1%, n=27), rosuvastatin (2.3%, n=3). No difference by age on statins used. Statins reduced LDL-C by 31% (mean 1.84mmol/L) compared with baseline. 55.6% of those treated still had levels over the European target of 3.5mmol/L. In n=102 children aged over 10 years not on statins: • no reasons recorded: 20%, n=20 • clinician considered child to be low risk: 37.2%, n=32 • first visit, trying lifestyle change: 17.4%, n=15	Adverse effects assessed after a mean 2.7 years statin treatment. **Markers of toxicity in those treated with statins (before statins vs after statins)** Liver enzymes: • ALT mean change from baseline (n=97): +1.61 U/L (95% CI 0.10 to 43.11), *p=0.008* • AST mean change from baseline (n=25): +0.52 U/L (95% CI -1.85 to +2.89), p=0.26 Creatinine kinase: • CK mean change from baseline (n=65): +7.6 U/L (95% CI -2.33 to +17.63), p=0.39 No individual had signs of toxicity as measured by a level >2.5 times the reference range. Muscle pain not routinely recorded in the register; not aware of any patients with statin-induced rhabdomyolysis. **Change in height and weight treated vs non-treated** Mean weight change during follow-up (n=80 statins, n=65 no statins): • +3.61kg statins vs +3.50kg no statins (p=0.97)

Study reference	Study design and objective	Population	Treatment	Outcomes
	reminders to provide annual follow-up.	• LDL-C (mean 5.88 vs 5.21mmol/l) • Weight (mean 42.1 vs 37.4kg) • Height (mean 1.45 vs 1.37m) NB no difference in BMI No difference in proportion with an identified gene variant (66.1% treated vs 67.8% untreated)	• starting statin after current visit: 14%, n=12 • awaiting DNA test or repeat lipids: 14.0%, n=12 • patient/parent/carer declined: 12.8%, n=11 • patient or parent intolerant: 2.3%, n=2 Alternative treatment: n=3 (2.2%) used resins, n=2 (1.6%) used plant sterols and a single person (0.8%) used ezetimibe. None were on fibrates.	• With adjustment for baseline age and sex: +3.58kg vs +3.53kg (p=0.91) Mean height change during follow-up (n=64 statins, n=46 no statins): • +4.26cm statins vs +4.87cm no statins (p=0.14) • With adjustment for baseline age and sex: +4.45cm vs +4.60cm (p=0.73) No child reported to have type 2 or type 1 diabetes.

Appraisal for quality and risk of bias

Quality assessments of included studies are reported below in Tables 20-24.

Criterion 5

Table 20. QUADAS-2 assessment of Wald et al (2016)[9]

Domain	Risk of Bias	Notes
Domain I: Patient selection		
Consecutive or random sample of population enrolled?	Low	
Case-control design avoided?	Low	
Inappropriate exclusions avoided?	Low	
Domain II: Index test		
Index test results interpreted without knowledge of reference standard results?	Low	TC level performed prior to FH48 panel testing and informed need for further DNA testing
Threshold pre-specified?	Low	
Domain III: Reference standard		
Reference standard likely to correctly classify condition?	Moderate	The complete testing of FH48, DNA sequencing (if negative), and 2 repeated raised cholesterols are likely to correctly define the condition among screen positives. Negatives were tested only for the FH48 panel which is likely to account for most variants, but there may be others identified through complete DNA sequencing
Reference standard results interpreted without knowledge of index test results?	Moderate	The reference standard would be objective but the TC level guided the reference standard performed.

Domain IV: Test strategy flow and timing		
Appropriate interval between index test and reference standard?	NA	
Did all participants receive the same reference standard?	Moderate	As above, potential verification bias
All patients included in analysis?	Moderate	No apparent loss to follow-up, though assumptions had to be made around expected results if all participants had received full DNA sequencing.
Domain V: Applicability		
Applicable to UK screening population of interest?	Low	
Applicable to UK screening test of interest?	Unclear	The screen test used is expected to be modified were it used in practice, to a lower TC threshold of >1.35 with reflex DNA testing which has not yet been tested.

Table 21. QUADAS-2 assessment of Futema et al (2017)

Domain	Risk of Bias	Notes
Domain I: Patient selection		
Consecutive or random sample of population enrolled?	Low	ALSPAC representative of general population of the region and random sample of those with blood tests were selected for sequencing.
Case-control design avoided?	Low	
Inappropriate exclusions avoided?	Low	
Domain II: Index test		
Index test results interpreted without knowledge of reference standard results?	Low	Historical cohort unclear sequence of index test and reference standard but objective and not expected to influence results.

Threshold pre-specified?	Low	
Domain III: Reference standard		
Reference standard likely to correctly classify condition?	High	High-depth targeted sequencing of the 3 genes was only performed for screen positives and a 4% random sample of screen negatives; uncertain whether low depth whole genome sequencing would have reliably identified all variants in screen negatives. Furthermore low depth sequencing was only performed for 30% of screen negatives.
Reference standard results interpreted without knowledge of index test results?	High	The reference standard would be objective but the cholesterol level guided the reference standard performed.
Domain IV: Test strategy flow and timing		
Appropriate interval between index test and reference standard?	NA	
Did all participants receive same reference standard?	High	As above, potential partial and differential verification bias.
All patients included in analysis?	High	Assumptions had to be made around expected results if all participants had received full DNA sequencing with extrapolation to the full cohort.
Domain V: Applicability		
Applicable to UK screening population of interest?	Low	
Applicable to UK screening test of interest?	Unclear	It is uncertain what threshold (TC or LDL-C) or method of DNA sequencing would be used in practice.

Criteria 11 and 13

Table 22. CASP systematic review checklist assessment USPSTF (2016) review[19, 23, 34]

NB. Assessment only for relevant questions on screening effects on FH-related morbidity and harms

Domain	Response	Notes
Validity of findings		
Focused question	Yes	Focused population, intervention and outcomes
Appropriate study inclusion	Yes	No restriction to study design excluding studies of non-applicable tests/populations
Relevant studies included	Yes	Thorough search across databases with ongoing surveillance
Quality assessment performed	NA	No studies identified
Was meta-analysis performed only when appropriate	NA	No studies identified
The results		
Clarity in the overall findings of the review and their presentation	NA	No studies identified
Precision of the results	NA	No studies identified
Applicability of the findings		
Applicability to the population of interest	Yes	Universal screening for dyslipidaemia by TC or LDL-C
Important outcomes considered	Yes	Relevant morbidity and harms outcomes
Benefits worth harms and costs	Unclear	Not possible to assess due to no evidence

Table 23. CASP systematic review checklist assessment of Vuorio et al (2017)[11]

Domain	Response	Notes
Validity of findings		
Focused question	Yes	Focused population, intervention and outcomes
Appropriate study inclusion	Yes	Focused on RCTs

Relevant studies included	Yes	Thorough search including unpublished literature and non-English language studies
Quality assessment performed	Yes	
Was meta-analysis performed only when appropriate	Yes	Results of individual studies given and discusses heterogeneity in pooled analyses
The results		
Clarity in the overall findings of the review and their presentation	Yes	
Precision of the results	Variable	There is moderate quality evidence for LDL-C levels with overall direction of effect, with heterogeneity which is likely explained by variation in statins used dose and duration. Other outcomes have limited or lower quality evidence and wide confidence intervals
Applicability of the findings		
Applicability to the population of interest	Yes	FH and representative of western populations
Important outcomes considered	Yes	Relevant morbidity and harms outcomes
Benefits worth harms and costs	Unclear	Can't say with certainty without longer term data

Criterion 13

Table 24. CASP cohort study checklist assessment of Humphries et al[12]

Domain	Response	Notes
Validity of findings		
Focused question	Yes	
Appropriate cohort recruitment	Yes	The study doesn't report the estimated proportion of children with FH (i.e. those who attend lipid clinics) who have been entered in the register, but there is no indication of biased or incomplete recording

Exposure accurately measured	Yes	Gives the total number in the register who were ever on statins and the number on statins at follow-up, details of drugs and doses given. Potential for error or incomplete entry but no obvious source of bias.
Outcome accurately measured	Unclear	Measures of AST, ALT and CK taken at follow-up. Subjective measures and no apparent sources of bias. However, measures don't appear to be taken for all children on statins with unclear reason.
Important confounders identified	Yes	The researchers have measured differences in baseline differences between those treated and not treated with statins. AST, ALT and CK are within-subject assessments that are likely to be influenced by statins; growth differences between treated and non-treated subjects have been adjusted for age and gender.
Confounders taken into account in design and analysis	Yes	As above
Follow-up complete	No	Apparently incomplete assessments for the full sample treated with and without statins, both for biochemistry and height and weight. Reasons unclear
Follow-up long enough	Unclear	Only 2-3 years on average, which may not indicate long-term effects
The results		
Clarity in the overall findings of the review	Yes	Results are clear and appropriate statistical comparison performed
Precision of the results	Yes	

Results believable	Unclear	No indication of bias or chance or flawed methodology – with the exception of uncertainty around completeness of results for all on statins
Applicability of the findings		
Applicability to the population of interest	Yes	FH and representative of the UK
Do the results fit with other available evidence	Yes	Findings are consistent with Vuorio et al Cochrane review
Implications for practice	Unclear	Despite potential incompleteness, this is reliable data on the safety of statins among children with FH in the UK, which is also supported by other evidence. Longer-term follow-up is, though, needed.

Appendix 5 — 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 25.

Table 25. 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
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.	6 to 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	12 to 21
		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.	19 to 20

		Method – briefly outline the rapid review methods used.	21 to 25
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*.	24 to 25
2.3	Appraisal for quality/risk of bias tool	Details of tool/checklist used to assess quality, e.g. QUADAS 2, CASP, SIGN, AMSTAR.	25
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.	21
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.	57 to 63
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.	24 to 25
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.	Study level reporting: 73 to 88 Quality assessment: 88 to 95

		For each study, present the results of any assessment of quality/risk of bias.	
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.	KQ1: 26 to 28 KQ2: 36 to 38 KQ3: 43 to 47
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.	KQ1: 29 to 34 KQ2: 39 to 41 KQ3: 47 to 52
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'?	KQ1: 35 KQ2: 42 KQ3: 54
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?	55
6.2	Limitations	Discuss limitations of the available evidence and of the review methodology if relevant.	56

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