Screening for familial hypercholesterolaemia in children and adolescents[1]

EXTRACT

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Key statement

Research question

The aim of this investigation is to assess the benefit of universal blood lipid screening for familial hypercholesterolaemia (FH) in children and adolescents compared with no screening.

Conclusion

Based on the available evidence, there is no hint of a benefit from universal blood lipid screening for FH in children and adolescents. There are no comparative intervention studies of the screening chain. When comparing earlier with later initiation of treatment (treatment with a fixed, average statin dose), a hint of a benefit can be inferred for earlier initiation. However, the underlying cohort study is not only subject to considerable risk of bias, but also does not allow conclusions to be drawn for universal lipid screening due to the selection of a high-risk population within the population with FH. Appropriate studies of the diagnostic accuracy of measuring blood cholesterol levels against the genetic reference standard are available. With a small number of affected individuals, these indicate a potentially low sensitivity (worst case approximately 20%).

Based on the above results of the cohort study on statin therapy, it can be concluded that the identification of children and adolescents with FH who are at high risk of an early-onset event makes sense in principle, as early initiation of statin therapy can reduce the risk of a cardiovascular event. The introduction of cascade screening, starting with affected family members (especially parents), should therefore be considered, especially as this is how the children in the cohort study were recruited. If cascade screening is introduced, it should be accompanied by a targeted, pragmatic and cost-effective evaluation embedded in the everyday health care setting. This evaluation should include a comparative study conducted in such a setting to address the open research question of the optimal time to start statin therapy. This rapid report outlines the initial considerations for such an accompanying evaluation.

Table of contents

List of tables

Page

List of figures

Page

List of abbreviations

Abbreviation	Meaning
ALSPAC	Avon Longitudinal Study of Parents and Children
ApoB	apolipoprotein B100
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e. V. (Association of the Scientific Medical Societies in Germany)
BMI	body mass index
CI	confidence interval
FH	familial hypercholesterolaemia
FP	false-positive
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HeFH	heterozygous familial hypercholesterolaemia
HoFH	homozygous familial hypercholesterolaemia
HR	hazard ratio
IMT	intima media thickness
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	intention to treat
LDL (-C / -R)	low density lipoprotein (-cholesterol / -receptor)
MoM	multiples of the median
PCSK9	proprotein convertase subtilisin / kexin type 9
PPV	positive predictive value
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
SR	systematic review
USPSTF	United States Preventive Services Taskforce
VOPT	verification of only positive testers

1 Background

Familial hypercholesterolaemia (FH) is a genetic lipid metabolism disorder that is inherited in an autosomal dominant manner [1,2]. A distinction is made between homozygous FH (HoFH) with altered alleles from both parents and heterozygous FH (HeFH), in which an altered allele is only inherited from one parent [3].

Various prevalence rates have been reported for HoFH (1:160,000 to 1:300,000 [4] and 1:250,000 to 1:1,000,000 [2]). Data on the prevalence of HeFH range from 1:200 to 1:500 [1,2,5,6].

The most common cause of FH is mutations in the low-density lipoprotein receptor gene (LDL-R gene) [1,2]. These cause a reduction in functional LDL receptors on the body cells, especially the hepatocytes, and thus a reduced uptake of LDL cholesterol from the blood into the cell [1,2,7]. Much more rarely, FH is caused by a mutation in the binding protein apolipoprotein B100 (ApoB), which restricts the binding of LDL cholesterol to the LDL receptor and thus also reduces the uptake of LDL cholesterol from the blood into the cell [2]. In addition, gain-of-function mutations in the proprotein convertase subtilisin / kexin type 9 gene (PCSK9 gene) are cited as an even rarer cause of FH [2]. Mutations of this type promote the degradation of LDL receptors, thus reducing the availability of functional LDL receptors and in turn causing a reduced uptake of LDL cholesterol from the blood into the cell [2].

As a result of these genetic disorders, increased LDL cholesterol levels occur in the blood in childhood [1,2,5,8]. While LDL cholesterol levels of over 200 mg/dl frequently occur in untreated HeFH, these can even exceed 500 mg/dl in HoFH [4], leading to increased cardiovascular morbidity and mortality due to the early onset of atherosclerosis [1,5,9]. It is reported that half of untreated men and a third of untreated women with FH will have cardiovascular event before the age of 50 (men) or 60 (women) [1]. Those affected with the very rare subtype of HoFH often suffer cardiovascular, sometimes fatal, events before the age of 20. In addition, in contrast to people with HeFH [8] they may already show lipid-specific physical signs such as xanthomas and arcus corneae in childhood, which often lead to a diagnosis.

In order to reduce or delay the risk of cardiovascular events, children and adolescents with known FH are treated early on with lipid-lowering treatments [8,10,11]. Statins are recommended as the drugs of first choice. Ezetimibe (alone or as a combination therapy) and anion exchange resins are also recommended as second-choice drugs for children and adolescents with HeFH. If appropriate, people with HoFH also receive LDL apheresis from around primary school age in addition to maximum drug therapy [4,5].

The laboratory diagnosis of FH is usually made by taking a blood sample and determining the level of LDL or total cholesterol. To date, however, there is a lack of generally recognized thresholds or defined criteria for the diagnosis of FH in children and adolescents [9]. One reason for this is that the thresholds for elevated cholesterol levels vary depending on the age of the person being tested and the family history (early cardiovascular events or hypercholesterolaemia in close family members) [9]. Furthermore, an increase in cholesterol levels can also be caused by additional factors or completely different causes (e.g. diet or other diseases). In 2 German observational studies on FH screening in children [12] and children and adolescents [13] a similar LDL level of ≥ 135 mg/dl or > 130 mg/dl was selected as the threshold for further diagnostic tests. In the case of elevated LDL levels, genotyping can be performed as a confirmatory test using molecular genetic tests, in particular to detect mutations in the LDL-R, ApoB or PCSK9 genes as the most common causes of FH [9].

There is currently no standardized procedure for identifying affected children and adolescents in Germany. According to the German Health Examination Directive [14] people insured by statutory health insurance (SHI) who are over the age of 18 and have an increased risk of FH (e.g. positive family history) are entitled to a lipid profile, including determination of LDL cholesterol. However, the introduction of universal screening by means of a blood cholesterol test in children and adolescents is being discussed (see e.g. [15-17]). The aim of such a universal screening for FH is to identify and treat people with FH at an earlier stage.

2 Research question

The aim of this investigation is to assess the benefit of universal blood lipid screening for familial hypercholesterolaemia (FH) in children and adolescents compared with no screening.

3 Methods

Comparative studies of the screening chain were included in the benefit assessment. If such studies were not available, or not available in sufficient quantity and quality, an assessment of intervention studies that enable a comparison of earlier versus later initiation of treatment, and of diagnostic accuracy studies as components of the screening chain (linked evidence) was planned.

Comparative intervention studies of the screening chain

The target population for the benefit assessment was children and adolescents (< 18 years). The test intervention was universal blood lipid screening for FH combined with earlier diagnosis and treatment. The control group was not screened for FH.

The following patient-relevant outcomes were considered:

- Mortality (especially all-cause mortality and cardiovascular mortality),
- Morbidity (especially cardiovascular events such as myocardial infarction and stroke),
- (Serious) adverse events - (S)AEs,
- Health-related quality of life.

Randomized controlled trials (RCTs) were to be included in the benefit assessment. If the evidence based on RCTs was insufficient for the benefit assessment, quasi-randomized controlled trials and prospective comparative cohort studies were also to be included. Studies with a minimum follow-up of 12 months after the start of treatment were included.

Comparative intervention studies on the start of treatment

If comparative intervention studies of the screening chain were not identified for the benefit assessment or were not identified in sufficient quantity and quality, studies that allowed a comparison of an earlier versus a later start of treatment (e.g. with statins) were also considered for the assessment. The target population of the intervention group consisted of children and adolescents (< 18 years) with a confirmed diagnosis of FH. The control group (also with a confirmed FH diagnosis) was to start treatment at least 5 years later (e.g. start in childhood vs. adolescence or adolescence vs. adulthood).

The above-mentioned patient-relevant outcomes were analysed for the assessment. RCTs were to be included in the benefit assessment. If no RCTs were available for the research question, studies with a lower level of evidence (quasi-randomized controlled trials, prospective and retrospective comparative cohort studies - possibly with a non-concurrent control group) were used for the benefit assessment. Another criterion for the inclusion of

studies was a minimum follow-up of 12 months after the start of treatment. Only studies published since 1995 were considered.

Diagnostic accuracy studies

If the earlier start of treatment resulted in a positive conclusion on its benefit (see section "Information retrieval, information assessment and synthesis"), diagnostic accuracy studies were also used for the benefit assessment. If no positive conclusion on the benefit of an earlier start of treatment was found, the diagnostic accuracy was nevertheless additionally considered in order to fulfil the need for information addressed in the commission with regard to relevant test accuracy criteria (including underlying cut-off values).

Studies with children and adolescents (< 18 years) were included in the assessment. All laboratory test methods used in the studies for lipid testing for FH using capillary blood or a venous blood sample were considered as the index test. Molecular genetic analyses were accepted as reference tests. In the case of unremarkable findings in the index test, follow-up was also accepted as an alternative. Prospective diagnostic cross-sectional and cohort studies with more than 1000 participants from which data could be derived to calculate the diagnostic accuracy with regard to the detection of FH were included. In addition, only studies published since the year 2000 were considered.

Information retrieval, information assessment and synthesis

Parallel to the preparation of the project outline, a search for systematic reviews (SRs) was carried out in MEDLINE (including the Cochrane Database of Systematic Reviews), the International Health Technology Assessment (HTA) Database and on the websites of the National Institute for Health and Care Excellence (NICE) and the Agency for Healthcare Research and Quality (AHRQ).

For each sub-question, it was examined whether at least 1 high-quality and current SR was available whose information retrieval could be used as the basis for the assessment (hereinafter: basic SR).

If such a basic SR was available for a sub-question, a supplementary search for studies for the period not covered by the basic SR was carried out in a second step. Otherwise, the search for studies was carried out without restricting the search period.

The systematic literature search for studies was carried out in MEDLINE, Embase and the Cochrane Central Register of Controlled Trials.

In addition, the following information sources were considered: study registries, reference lists of identified SRs, and author enquiries.

The selection of relevant studies was carried out by 2 reviewers independently of each other. Discrepancies were resolved by discussion between them. Data were extracted into standardized tables. Across-outcome and outcome-specific risk-of-bias criteria were assessed to evaluate the qualitative certainty of results (shortened to “certainty of results” in the following text), and the risk of bias was rated as low or high in each case. For diagnostic accuracy studies, in addition to the risk of bias of the results, the transferability to the German health care setting was also examined. The results of the individual studies were described according to outcomes.

In addition to the comparison of the results of the individual studies, meta-analyses and sensitivity analyses were performed and effect modifiers examined, provided that the methodological requirements were met.

Across outcomes, a conclusion on evidence of (greater) benefit and (greater) harm was made in 4 grades regarding the respective certainty of conclusions: either proof (highest certainty of conclusions), an indication (moderate certainty of conclusions), a hint (weakest certainty of conclusions), or none of these 3 situations was present. The latter case occurred when no data were available or the available data did not allow any of the other 3 conclusions. In this case, the conclusion “There is no hint of (greater) benefit or (greater) harm” was drawn.

In the case of an assessment based on studies with a lower evidence level (retrospective comparative cohort studies - possibly with a non-concurrent control group) and a resulting low or very low certainty of results, a positive conclusion on the benefit of bringing forward treatment was only possible if the effects shown were so large that they could not be explained solely by the influence of confounders (dramatic effect). In the linked evidence approach, the benefit of screening was derived by comparing the health-related consequences of the possible test results and their probabilities together with a conclusion on the benefit of starting treatment earlier. In this way, the certainty of conclusions with regard to the benefit of screening took into account both the certainty of conclusions with regard to the benefit of starting treatment earlier and with regard to diagnostic accuracy.

4 Results

4.1 Results of information retrieval

For the sub-questions on "comparative intervention studies of the screening chain" and on "diagnostic accuracy studies", 1 SR each was considered as a basic SR for the purpose of identifying primary studies. No SR was considered for the sub-question on "comparative intervention studies on the start of treatment".

The information retrieval revealed no comparative intervention study of the screening chain relevant to the research question. No planned or ongoing study was identified. The search strategies for bibliographic databases and study registries can be found in the appendix. The last search for studies in the screening chain took place on 5 March 2024.

The information retrieval revealed 1 retrospective comparative cohort study (5 documents) on the start of treatment that was relevant to the research question. The study included a non-concurrent control group. In this study, a group of patients with HeFH who started statin therapy in childhood and adolescence were compared with their parents who were also affected by FH and for whom no statin therapy had been available in childhood and adolescence. No relevant studies were found on other treatment options (e.g. ezetimibe, lifestyle and dietary changes or LDL apheresis), on the comparison of starting treatment in childhood versus adolescence, or on a study population with HoFH. No planned or ongoing study was identified.

The search strategies for bibliographic databases and study registries can be found in the appendix. The last search for studies on the start of treatment took place on 28 March 2024.

The information retrieval revealed 3 diagnostic accuracy studies relevant to the research question. Of these, 2 studies were used for the present assessment, as they have a higher informative value due to the verification of all subjects examined than the third study with a "verification of only positive testers" (VOPT) design, i.e. the verification of only index test-positive subjects. One ongoing study and 2 studies with an unclear status were identified.

The search strategies for bibliographic databases and study registries can be found in the appendix. The last search for diagnostic accuracy studies took place on 3 April 2024.

Table 1: Study pool of the benefit assessment

Study	Available documents			
	Full publication (in scientific journals)	**Registry entry / results report from study registries**	**Other documents**	**Study included in the benefit assessment**
Comparative intervention studies of the screening chain				
No relevant studies identified				
Comparative intervention studies on the start of treatment				
Luirink 2019	[18-22]	no	no	yes
Diagnostic accuracy studies				
Futema 2017	[23]	no	no	yes
Sustar 2022	[24]	yes [25] / no	no	no[a]
Forest 2016	[26]	no	no	yes

a. The reference test was conducted exclusively for the test-positive results of the index test (VOPT). As the evidence from studies that verify both positive and negative results in the index test with the reference test (complete verification) is sufficient, the study in the VOPT design is not used for the benefit assessment (see Section A2.3.5 of the full report).

VOPT: verification of only positive testers

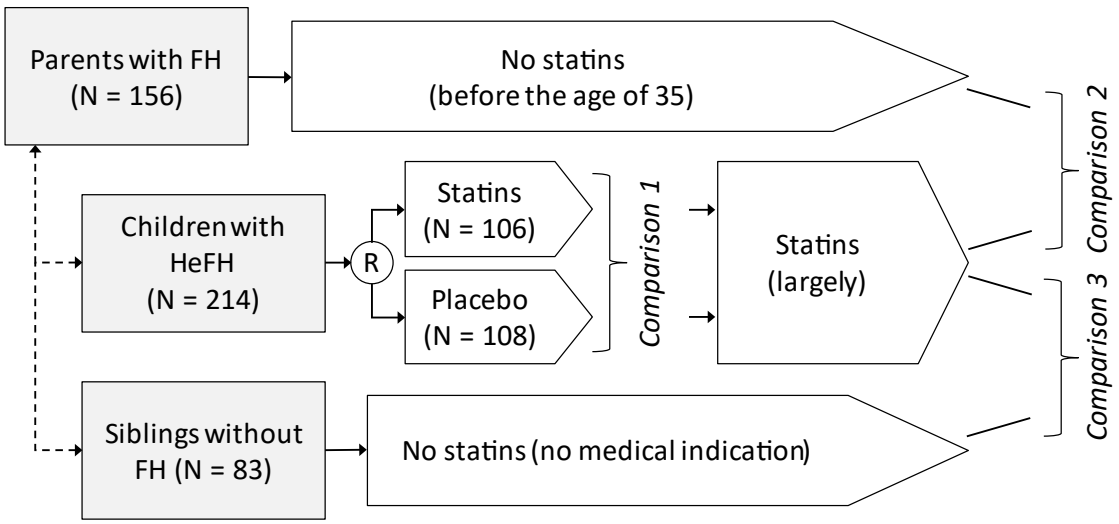
4.2 Comparative intervention studies of the screening chain

Comparative intervention studies of the screening chain could not be identified. Therefore, the individual components of the screening chain were assessed - on the one hand on the basis of comparative intervention studies on the start of treatment (see Section 4.3), on the other hand on the basis of diagnostic accuracy studies (see Section 4.4).

4.3 Comparative intervention studies on the start of treatment

4.3.1 Characteristics of the studies included in the assessment

To compare earlier versus later treatment initiation, 1 retrospective comparative cohort study with a non-concurrent control group (Luirink 2019 [21]) was included. The intervention group (N = 214) of this comparison consisted of the entire study population, i.e. the test and control group of a previous RCT [22] which was followed up for 20 years in a longitudinal study (Figure 1). The control group consisted of parents of people in the intervention group who were also affected by FH (N = 156). Both groups are described separately below.



FH: familial hypercholesterolaemia; R: randomization; dashed line: family relationship

Figure 1: Simplified presentation of the Luirink 2019 study with its 3 comparisons

For the previous RCT (on which the intervention group was based) (Comparison 1 in Figure 1), a total of 214 children and adolescents aged between 8 and 18 years with previously untreated HeFH were consecutively enrolled in the Netherlands. Prerequisites for inclusion in the study were 2 fasting samples with LDL-C levels ≥ 155 mg/dl and triglyceride levels < 350 mg/dl as well as a previous 3-month low-fat diet. The study population had been identified by cascade screening after a molecular-genetic or clear clinical FH diagnosis of at least 1 parent. Genetic verification of HeFH was available for 98% of the study population. Children and adolescents with HoFH were excluded from the study. People in the intervention group started taking pravastatin from an average age of 14 years (SD: 3.1). The daily dosage with evening intake was 20 mg (< 14 years) and 40 mg (≥ 14 years). The children in the control group received placebo, but were able to switch to statins after 2 years. At the time of analysis, 20 years after the start of observation of the study population, the people included as children and adolescents were on average 31.7 years old and the majority (79%) stated that they were still taking lipid-lowering medication.

Only little information was available on the control group of the cohort study (Comparison 2 in Figure 1). As already mentioned, these were the parents of the subjects in the intervention group who were also affected by FH. How they were originally identified (e.g. via lipid screening, via a chance finding or due to a cardiovascular event) is not reported. Furthermore, in addition to missing characteristics such as comorbidities, it is not known whether these were exclusively people with HeFH or whether parents with HoFH and a correspondingly

higher risk of very early cardiovascular events were also included in the analysis. In addition, no information was given about the parents' treatment - neither how long they had been treated nor what type of treatment they had received (e.g. statins or other treatments). As statins have only been available since 1988, the parents could not have started statin therapy before the age of 32.

Overall, this (non-prospectively planned) comparison of the intervention group treated with statins at an early age and the affected parents as a non-concurrent control group allows, in principle, an assessment of starting statin therapy in childhood or adolescence versus starting it (at the earliest) in adulthood.

In the retrospective comparison, all-cause and cardiovascular mortality as well as cardiovascular events (including myocardial infarction, stroke and coronary revascularization) were reported as outcomes. Information on SAEs (including rhabdomyolysis) was only available for the intervention group with statin therapy from childhood and adolescence. In addition, there was a comparison of the intervention group with their age-matched siblings not affected by FH [20,21]. This comparison (Comparison 3 in Figure 1) provided information on the potential harm of starting statin therapy early in terms of possible developmental and growth disorders.

4.3.2 Overview of patient-relevant outcomes

From the documents of the included Luirink 2019 study, results on the patient-relevant outcomes of all-cause mortality, cardiovascular mortality and cardiovascular events and SAEs (including rhabdomyolysis) were usable (see Table 2).

Table 2: Matrix of patient-relevant outcomes

Study	Outcomes						
	Mortality		Morbidity	QoL	Side effects		
	All-cause mortality	Cardiovascular mortality	Cardiovascular events	Health-related quality of life	SAEs	Rhabdomyolysis	Developmental and growth disorders
Luirink 2019	●[a]	●[b]	●[b]	-	●[c]	●[c]	●[d]

●: Data were reported and were usable.
-: No data were reported (no further details) / The outcome was not recorded.
a. Analysis time for all-cause mortality: 10 years after the start of observation of the intervention group (no data is available at 20 years after the start of observation).
b. Analysis time for cardiovascular mortality and cardiovascular events: 20 years after the start of observation of the intervention group.
c. Data on SAEs, including rhabdomyolysis, are only available for the intervention group.
d. The data from the intervention group were compared with the data from the siblings not affected by FH.
FH: familial hypercholesterolaemia; QoL: quality of life; SAE: serious adverse event

4.3.3 Assessment of the risk of bias of the results

Due to the retrospective study design with the parents as a non-concurrent control group, the risk of bias for this comparison can be rated as high across all outcomes. The outcome-specific risk of bias of this comparison was therefore also rated as high for all associated outcomes. Therefore, the certainty of results for these outcomes was rated as very low.

The risk of bias of the prospective comparison of the data of the intervention group with that of their age-matched siblings without FH was also rated as high across all outcomes. This is mainly due to the lack of reporting of (in part primary) outcomes such as cardiovascular morbidity, which should have been recorded according to the study protocol. Therefore, the outcome-specific risk of bias for the outcome “development and growth disorders” was also rated as high and the certainty of results for this outcome was rated as very low.

4.3.4 Results on patient-relevant outcomes

4.3.4.1 Results for all-cause mortality

For all-cause mortality, results are only available up to the age of 30. It was reported that only 1 (0.5%) of the 214 subjects recruited as children/adolescents had died (due to a traffic accident at the age of 15), whereas a total of 14 affected parents and thus 9% of the control group had died by this age. As no (possibly adjusted) effect measure was reported for these

events taking into account the "time under risk" and not all subjects in the intervention group were followed up until the age of 30, these results can only be interpreted to a limited extent.

A large part of the all-cause mortality in the parent group can be explained by cardiovascular mortality. In the following Section 4.3.4.2, possible confounders are listed which, in addition to the missing effect measure, must be taken into account both in the interpretation of the numerical difference in cardiovascular mortality and in the interpretation of the numerical difference in all-cause mortality.

4.3.4.2 Results on cardiovascular mortality

For cardiovascular mortality, it was reported that before their 40th birthday, none of the subjects included as children and adolescents had died due to a cardiovascular event. In contrast, a total of 11 cardiovascular-related deaths were reported for the parents. This corresponds to 7% of the control population. As no (possibly adjusted) effect measure was reported for these events taking into account the "time under risk" and not all subjects in the intervention group were followed up until the age of 40, these results can only be interpreted to a limited extent.

When interpreting this numerical difference, at least the following possible major problems of internal and external validity must also be taken into account:

- Bias due to selection of study participants: Selection bias can be assumed because parents are more likely to agree to their child participating in a study if they themselves are already more severely affected by the disease. Statin therapy for children was not yet standard around 1999, so that parents who had already suffered a cardiovascular event in particular are likely to have agreed to possible statin therapy for their child as part of a study. 26% of the affected parents in the Luirink study had already suffered from cardiovascular morbidity before the age of 40 (see Section 4.3.4.3 below) and 7% had even died before the age of 40. A negative selection of such severely affected parents may seriously distort the comparison with the children.
- Insufficient transferability: However, it is also likely that the selection of particularly severely affected families represents certain subtypes of HeFH in a typical manner and therefore does not represent a negative selection in this respect. However, these particularly severe forms of HeFH are then no longer representative of the totality of all forms of HeFH that would be identified by lipid screening. Accordingly, the mortality and morbidity differences reported in the Luirink 2019 study very likely represent an overestimation of the true effects of early statin therapy in the totality of those affected by FH. In the context of different forms of FH, it is even possible that individual affected parents in the Luirink study did not have heterozygous but homozygous FH. This is because the children could be included in the study if one parent had a molecular

genetically confirmed or clinical FH diagnosis. Enquiries to the authors regarding the possible inclusion of parents with HoFH remained unanswered.

- Bias due to unequal concomitant interventions: From the publicly reported figures on causes of death in Germany, it can be deduced, among other things, for the period from 1991 to 2019 that cardiovascular-related deaths among people between the ages of 25 and 45 more than halved [27]. Even assuming a general population decline in this age cohort, the considerable decrease in cardiovascular-related deaths suggests that the overall care of myocardial infarctions or strokes also improved during this period and that this could have increased the survival probability of people with cardiovascular events (possible performance bias).
- Bias due to confounders: In the comparative analyses, relevant confounders such as concomitant diseases (e.g. diabetes or lipid-independent cardiovascular diseases), body mass index (BMI) or disease-specific risk factors (e.g. elevated lipoprotein(a) levels) are not taken into account in the analysis (possible bias due to confounding). The analysis of cardiovascular events (see Section 4.3.4.3) was adjusted for sex and smoking status. Overall, however, adjustment for 2 confounders still leaves a great deal of room for bias, as this is not a parallel group comparison.

Although the numerical difference between the two populations is large, it is possible that the aspects mentioned explain a large part of the difference in cardiovascular mortality. However, a conclusion on the evidence for this outcome is not possible, if only because of the lack of a (time-dependent) effect measure.

4.3.4.3 Results on cardiovascular events

For the morbidity outcome of cardiovascular events, it was reported that before their 40th birthday, only 1 person in the intervention group included as children and adolescents experienced a cardiovascular event. This was an angina pectoris event at the age of 28.6 years, which was treated by means of percutaneous coronary intervention. The subject was a non-smoker and had stopped taking statins at the end of the original study. For the parents as the control group, it was reported that a total of 41 people had a cardiovascular event for the first time before the age limit of < 40 years. This corresponds to 26% of the control group. Of these, 27 people suffered a myocardial infarction and 7 people suffered angina pectoris. The cardiovascular events of the remaining 7 parents with an event were not explained. These results yielded a statistically significant hazard ratio (HR) (adjusted for sex and smoking status) of 0.08 (95% confidence interval [CI]: [0.01; 0.33]) for the comparison of the subjects included as children and adolescents and treated with statins at an early stage with the affected parents.[2]

[2] In the publication [21], the HR [95% CI] of the affected parents versus the intervention group treated with statins at an early age was given as 11.8 [3; 107]. The reciprocal value is used here.

When interpreting this large difference, at least the 4 previously mentioned problems of external and internal validity (Section 4.3.4.2) must be taken into account. It can therefore be assumed that the reported difference in the outcome of cardiovascular events between the early intervention group and the parental control group is subject to such uncertainty that it remains unclear whether the effect is due solely to problems with the study design.

4.3.4.4 Results on adverse events

No data were reported on AEs for the parental control group and therefore no comparison was possible. For the intervention group, it was stated that no rhabdomyolysis and no other SAEs had occurred by the end of the 20-year follow-up period.

4.3.4.5 Results on development and growth disorders

No data were reported on developmental and growth disorders for the parental control group and therefore no comparison was possible.

For this outcome, however, the available information on the physical and mental development of the intervention group (N = 194) was compared with data from their unaffected siblings (N = 83). This comparison (Comparison 3 in Figure 1) did not reveal any relevant group differences with regard to developmental and growth disorders after a follow-up period of 10 and 20 years. For example, the mean age at onset of menarche, mean height and BMI as well as the proportion of people with a high, medium or low level of education were comparable between the subjects with early statin therapy in the intervention group and their siblings at both 10 and 20 years. Overall, the data indicate that statin therapy starting in childhood and adolescence is not associated with any harm (e.g. impairment of hormonal or mental development) with regard to the characteristics analysed.

4.4 Diagnostic accuracy studies

Irrespective of a positive conclusion on the benefit of starting treatment earlier, this report looks at diagnostic accuracy in order to fulfil the need for information regarding relevant test accuracy criteria (including underlying cut-off values) addressed in the commission.

A total of 3 studies were included for diagnostic accuracy; in 2 of these studies (Futema 2017 [23], Wald 2016 [26]) all children received the reference test ("complete verification") and thus a conclusion on sensitivity and specificity, among other things, was possible. In the third study (Sustar 2022 [24]), a VOPT was carried out, i.e. the children with a negative index test result did not receive a reference test for verification and were not systematically followed up. Therefore, only the positive predictive value (PPV) could be derived from the data. Conclusions on the other test accuracy criteria such as sensitivity or specificity were not possible. Therefore, the study with a VOPT design (Sustar 2022 [24], with determination of the PPV for a subpopulation of 813 children with a positive index test) was not considered in

this report. Neither the certainty of results was assessed nor were data on study characteristics or results extracted.

4.4.1 Characteristics of the studies included in the assessment

The characteristics of the Futema 2017 and Wald 2016 studies are described below.

In the Futema 2017 study [23] is a sub-population analysis of the prospective cohort study "Avon Longitudinal Study of Parents and Children" (ALSPAC), in which population-based data from children in the United Kingdom were systematically collected. Among other things, the LDL cholesterol of 5083 of these children, most of whom were recruited prenatally between April 1991 and December 1992, was determined from the total cholesterol at the age of approx. 10 years using the Friedewald formula. For a random sample of the ALSPAC population (UK10K project: N = 1503), molecular genetic testing for FH was carried out in addition to the determination of LDL cholesterol. In Futema 2017, the data of 1497 of these children were retrospectively analysed with regard to the diagnostic accuracy of the determination of LDL cholesterol. The LDL-C levels determined were converted into multiples of the median (MoM) as a measure of the relative deviation of an individual value from the median of the overall population. A MoM of LDL-C ≥ 1.84 MoM (corresponds to ≥ 164 mg/dl or ≥ 4.25 mmol/l) was considered a positive test result. The molecular genetic testing for FH included a low-read depth sequencing of the entire genome for the entire sub-population. For 55 of these children, who were randomly stratified from the quartiles of the LDL distribution of the blood samples, targeted high-read-depth sequencing of known FH genes (LDL-R, APOB and PCSK9) was also performed, for which all identified variants were verified using Sanger sequencing. The latter high-read-depth sequencing was also carried out for the samples of 15 other children who were not part of the UK10K project sub-population, but were selectively added by the group of authors. As they therefore do not fulfil the inclusion criteria formulated for the report, the results of these 15 children are not included in the present assessment.

In a prospective diagnostic cohort study, Wald 2016 [26] describes the results of a screening programme for FH in the United Kingdom. Between March 2012 and March 2015, parents were offered screening for FH for their children in 92 general practices. This was to take place at around 1 year of age as part of the routine vaccination programme. Capillary blood samples were taken from the heel of the 10,095 children analysed at the same time as the vaccination was administered, which were used for the direct determination of total cholesterol and for molecular genetic testing for FH. The MoM was calculated for each cholesterol value measured. A MoM of total cholesterol ≥ 1.53 MoM (corresponding to ≥ 230 mg/dl or ≥ 5.95 mmol/l) was considered a positive test result. After DNA extraction, the molecular genetic test included an analysis for 48 mutations of FH (FH48) including the 46 mutations of the LDL receptor most frequently detected in the regional genetic laboratory between 2001 and 2010 as well as one specific mutation each of APOB and PCSK9. If none of these 48 mutations were

detected, further DNA analysis was carried out using Sanger sequencing of LDL-R, APOB and PCSK9, provided the previously determined MoM for total cholesterol was ≥ 1.53. For this report, positive results in FH48 or in the further DNA analysis by means of Sanger sequencing are used as reference-standard positive. A further operationalization to determine the presence of FH reported in Wald 2016, which does not include a molecular genetic finding but is based on the repeated determination of total cholesterol, is not taken into account in the present assessment as it does not meet the inclusion criteria for the reference standard formulated for the report.

4.4.2 Overview of outcomes relevant for the assessment

Two studies were used to assess suitable diagnostic test procedures (Futema 2017 and Wald 2016). These 2 studies on the diagnostic accuracy of universal screening for FH using a laboratory cholesterol test in children and adolescents allowed the sensitivity, specificity and PPV to be calculated for the respective study.

4.4.3 Assessment of the risk of bias and the transferability of the results

In both studies analysed, a high risk of bias was identified. In the Futema 2017 study, the risk of bias resulting from patient flow and study schedule was assessed as high, as not all children received the same reference standard and the reporting of the patient flow was inaccurate. The assessment result of this QUADAS domain also applies to the Wald 2016 study. Here, too, not all children received the same reference standard. In addition, not all test results could be included in the analysis. Furthermore, in Wald 2016, the risk of bias of the reference test was assessed as high, as the further DNA analysis (for index test positives with a negative first molecular genetic test) was carried out and analysed with knowledge of the results of the index test.

The concerns regarding the transferability of the results were assessed as low for both studies.

4.4.4 Results for parameters relevant for the assessment

For LDL cholesterol testing as an index test in children aged approx. 10 years and a cut-off of LDL-C ≥ 1.84 MoM,[3] the Futema 2017 study showed a sensitivity of 66.7% (95% CI: [20.8; 93.9]) and a specificity of 100% (95% CI: [99.7; 100]). Two out of 1497 children tested positive via measurement of LDL cholesterol. Of these, no child proved to be false-positive in the reference test (PPV: 100%; 95% CI: [34.2; 100]).

The Wald 2016 study showed a sensitivity of 54.1% (95% CI: [38.4; 69.0]) and a specificity of 99.3% (95% CI: [99.1; 99.4]) for total cholesterol testing as an index test in children aged around 1 year and a cut-off of total cholesterol ≥ 1.53 MoM (corresponds to ≥ 230 mg/dl or ≥

[3] corresponds to ≥ 164 mg/dl or ≥ 4.25 mmol/l

5.95 mmol/l). A total of 72 children proved to be false-positive (PPV: 21.7%; 95% CI: [14.5; 31.2]). Since, in the case of an initially negative result of the reference standard (FH48), only those children who had a total cholesterol of ≥ 1.53 MoM received further DNA analysis by means of Sanger sequencing and thus an unequal reference standard was used between index test positives and index test negatives, the values for sensitivity and specificity represent an overestimation, which is particularly relevant for sensitivity. However, this step-by-step molecular genetic testing corresponds most closely to the reality of health care, which is why the possibility of presenting diagnostic accuracy exclusively on the basis of FH48 testing was waived.

Due to the different tests (LDL-C or total cholesterol), a meta-analysis of the respective results is not meaningful.

In summary, the PPVs determined from the 2 studies differ markedly. However, the informative value of the markedly higher estimate of the Futema 2017 study is limited due to the comparatively low number of children examined compared to Wald 2016, which is particularly evident in the range of the CI (95% CI: [34.2; 100]). Nevertheless, the clear difference between the two PPV values suggests that LDL-C would be more favourable than total cholesterol as a screening test.

The specificity of both test procedures is very high, ensuring that the majority of unaffected children are correctly diagnosed as not having FH.

However, both studies show a markedly lower point estimate for sensitivity with wide (Wald 2016: 95% CI: [38.4; 69.0]) or very wide (Futema 2017: 95% CI: [20.8; 93.9]) CIs. It can be assumed that the lipid screening carried out in both studies identified children with FH who would remain at least partially unrecognized in the current health care setting without screening. However, the data imply that a considerable proportion of FH-affected children would not be recognized through universal blood lipid screening if the test procedures (and cut-off values) used in these studies were applied. In the worst case scenario, this would apply to 4 out of 5 children affected by FH. Such false-negative screening results can cause delayed diagnosis and treatment delays. It is conceivable, for example, that people affected or medical staff would not follow up on a suspicion of FH due to the negative screening result, or would delay further clarifying diagnostic tests until further tests of lipid levels or the presence of disease-specific symptoms. The extent to which this harbours a potential for harm for those with FH that exceeds the possible advantage for individuals correctly classified with FH and the very high specificity cannot be assessed on the basis of the available data.

Overall, due to the low statistical precision of the data on sensitivity, the results on test accuracy are too uncertain to be able to derive a conclusion on the suitability of the test methods for universal blood lipid screening for FH.

4.5 Summarized assessment of the results

Evidence map

Due to the lack of studies on the entire screening chain, no evidence map is presented.

Assessment of the scope of unpublished data

The study registry search only found ongoing diagnostic accuracy studies (see Section 4.1) whose planned end date had been exceeded only a few months before (EARLIE [28,29]) or was in the future (NCT04529967 [30] and VRONI [13,31]). Since all 3 studies were VOPT studies and 2 studies with complete verification could be included in the benefit assessment, it cannot be assumed that further relevant results for the present research question will emerge after publication of these study results. The information retrieval showed no signs of possible unpublished study data or publication bias. However, this can only be assessed to a limited extent due to the lack of mandatory registration of non-randomized studies.

Weighing up the benefits and harms

No comparative intervention studies of the screening chain could be identified.

For the comparison of an earlier versus a later start of treatment, usable long-term data are available for people with HeFH who started statin therapy as children and adolescents at an average age of 14 years and were followed up into adulthood. In a retrospective comparison, their data were contrasted with the data of their parent(s) (also affected by FH) as a control group that was not concurrent and for whom statin therapy was possible from the age of 32 at the earliest. This comparison shows a statistically significant advantage for the morbidity outcome of cardiovascular events in favour of starting statin therapy earlier from childhood and adolescence compared to starting statin therapy later in adulthood. For both cardiovascular mortality and all-cause mortality, there is a numerical difference in favour of starting statin therapy earlier. However, these two differences can only be interpreted to a limited extent, as no (time-dependent) effect measure was reported for either outcome. Furthermore, in a non-randomized study with non-concurrent groups, considerable risk of bias due to subject selection (selection bias), co-interventions (performance bias) and confounders (confounding bias) is to be expected (see Section 4.3.4.2).

Above all, however, it cannot be ruled out that the intervention group selected via the parents is an FH subpopulation that is not representative of the spectrum of people with FH identified via universal screening with regard to the initial risk of cardiovascular events. It is therefore possible that a treatment effect of statins in this subpopulation is not fully transferable to other people with FH. For people who started statin therapy as children and adolescents, no potential for harm was shown with regard to starting treatment earlier, neither in terms of SAEs (including rhabdomyolysis) nor in terms of possible developmental and growth disorders.

The interim conclusion is that early statin therapy is beneficial in certain children and adolescents affected by HeFH, but that, without additional evidence, this result cannot be transferred to the totality of all children and adolescents with HeFH relevant in the screening context.

No results are available for other outcomes such as health-related quality of life, for people with specific risk factors (e.g. people with HoFH, highly elevated lipoprotein(a) levels or comorbidities such as diabetes) or for other treatment options (e.g. ezetimibe, lifestyle and dietary modifications or LDL apheresis).

Two studies were available on diagnostic accuracy, in which all children received a molecular genetic reference test ("complete verification") and thus enabled a conclusion to be made on sensitivity and specificity, among other things. In both included studies, the point estimate shows a low sensitivity of 54.1% (threshold for total cholesterol ≥ 230 mg/dl) and 66.7% (threshold for LDL-C ≥ 164 mg/dl). In the worst case scenario, 4 out of 5 FH-affected children could be overlooked due to a false-negative result if LDL cholesterol is used as an index test. The risk of delayed diagnosis and treatment delays associated with such a false-negative screening result could be detrimental to those affected, as they may mistakenly believe not to be affected by FH. The extent to which this exceeds a possible advantage for correctly classified people with FH and the very high specificity with a predominant avoidance of false-positive findings cannot be assessed based on the available data. It is true that sensitivity could be increased by lowering the threshold. However, this would also increase the rate of false-positive findings and lead to a higher number of worrying "false alarms" in people not affected by FH. This could in turn lead to a high number of non-FH-related lipid elevations being permanently monitored and treated – beyond the actual intention of FH screening.

Overall, due to the low statistical precision of the data on sensitivity, the results on test accuracy are too uncertain to be able to derive a conclusion on the suitability of the test methods for universal blood lipid screening for FH.

When the available results on the start of treatment and on the diagnostic accuracy using the linked evidence approach are combined, overall, there is no hint of a benefit of universal blood lipid screening for FH versus no screening in children and adolescents. The effects in favour of statin therapy started in childhood and adolescence are subject to great uncertainty. Above all, however, it is unclear whether the results can be transferred to the people with FH detected in a comprehensive screening programme. In addition, the results on the sensitivity of the test methods examined in the diagnostic studies are too uncertain to be able to derive a conclusion on their suitability for universal blood lipid screening for the early detection of FH.

5 Classification of the assessment result

There is currently no systematic FH screening in childhood in Germany. In addition, testing for FH in the optional check-up in adolescents (J1) is inconsistent and sometimes unspecific. For this reason, the majority of affected individuals with FH requiring treatment are currently only identified when specific symptoms such as xanthomas or even cardiovascular events occur [32]. FH screening would therefore lead to more diagnoses, but above all, it would bring forward the diagnosis of many affected individuals by around 20 to 40 years. In contrast, for people who attend regular health check-ups after reaching adulthood and are identified there via the measurement of lipid levels, bringing forward the diagnosis would only make a difference of around 10 years.

The study setting in Luirink 2019 for the 20-year comparison of the people recruited as children and adolescents and the affected parents with FH reflects the current health care setting in Germany quite well. It also represents the best currently available evidence for evaluating the effects of bringing forward treatment. Another positive aspect of the setting of the Luirink 2019 study was that the family connection between the children and adolescents and their parents suggests that this comparison shows fewer differences in terms of lifestyle, diet and relevant environmental factors as well as potential genetic dispositions than a comparison of the intervention group with an independent, unrelated control population. However, due to the lack of information on the characteristics and treatment of the parental control group, among other things, the results of the study are not suitable for quantifying or transferring the reported group differences with sufficient certainty. In the comprehensive literature search, no other studies were identified that reported a similar approach. Nor are any future study results expected that will investigate such a comparison with the required similar length of follow-up in a randomized study design. Due to the available data on the efficacy of statins and the established treatment standards, the required treatment delay in the control group without statin therapy seems no longer feasible.

It is remarkable that in the Luirink 2019 study, the 194 children affected by HeFH did not reach the target levels recommended in some guidelines despite treatment, but still showed such low morbidity and mortality over the long-term course. In the 10 -and 20-year- follow-up examinations, the mean LDL-C level was 173 mg/dl [20] and 161 mg/dl respectively [21]. This is well above the LDL-C target levels of 55 and 70 mg/dl, which should at least be achieved for very high and high risk individuals, respectively, according to the 2019 ESC-EAS dyslipidaemia guideline [33]. Thus, the results of the Luirink study do not support the "the-lower-the-better" approach propagated in many guidelines, but on the contrary suggest that a fixed average dose of a statin is sufficient as standard therapy for cardiovascular protection.

Evidence on FH screening in Germany

In the course of searching for diagnostic accuracy studies, 2 studies were identified that are investigating FH screening in Germany. In the ongoing VRONI study [13,31] which started at the beginning of 2021, a total of 50,000 Bavarian schoolchildren between the ages of 5 and 14 are being tested for elevated cholesterol levels (in particular as part of the paediatric U9 to J1 screenings). The children and adolescents with LDL-C levels > 130 mg/dl from capillary or venous blood samples undergo a molecular genetic test to verify an underlying variant for FH. Individuals with LDL-C levels below the threshold are not followed up. The study is therefore based on a VOPT design, which is why no information on sensitivity and specificity can be obtained from it. Apart from data on the PPV and the rate of identified children with FH, it is therefore unlikely to provide any relevant new findings on diagnostic accuracy compared to the studies used in this benefit assessment. According to a recent article [16], which cites interim results of the VRONI study presented at a conference, more than 19,000 of the 50,000 children targeted have been screened to date. In 7.2% of these 19,000 children, an elevated LDL-C level was detected and 222 children (corresponding to 1.1% of all children screened) were diagnosed with FH. According to our own calculations, this corresponds to a PPV of 15 to 16%, i.e. only 15 to 16 out of 100 children with a positive index test in a screening as defined for VRONI (threshold LDL-C = 130 mg/dl) would actually be diagnosed with FH. These preliminary results of the VRONI study thus differ markedly from the results of the Futema study, in which in the point estimate a PPV of 100% was achieved with a markedly higher threshold (LDL-C ≥ 164 mg/dl). To date, no information is available from the VRONI study on the consequences of an elevated LDL-C value for those affected if FH is excluded. Even if the VRONI study has no direct relevance for the present benefit assessment due to its design, realistic results on possible screening consequences would be helpful.

For the Fr1dolin study [12,34,35], the results of more than 15,000 children examined in Lower Saxony and Hamburg have already been published. In this study, screening was carried out between the ages of 2 and 6 years (median: 3.9 years) using capillary blood sampling. A value exceeding the LDL-C threshold of 135 mg/dl (corresponding to the 95% percentile) was found in around 5% of the children examined. About 1% of the children had an LDL-C level of > 160 mg/dl (corresponding to the 99% percentile). Children with LDL-C levels above 135 mg/dl underwent a second LDL-C measurement. If the threshold was exceeded again, the child was referred to a specialist paediatric outpatient clinic for lipid disorders with optional molecular genetic verification of FH. In this study too, children with lower LDL-C levels below the threshold were not followed up and genetically analysed. Information on FH prevalence or PPV could not be derived from the data. Due to the only optional and thus missing systematic verification by means of a genetic test, the study was not included for assessment in this report (see Section A6.3.3 of the full report).

Discussion of thresholds, the relevance of false-positive findings and overdiagnosis

In the diagnostic accuracy studies used for the present assessment, different methods were selected for carrying out the index test (see Section 4.4). While total cholesterol was used as the assessment parameter in Wald 2016, the study organizers in Futema 2017 used LDL-C levels, which are more advantageous in terms of test accuracy, to determine FH. If a screening measure is primarily intended to produce a high detection rate of people with FH, a lower threshold would tend to be selected for the index test. This would increase the sensitivity and thus the rate of true-positive findings. However, this would inevitably be accompanied by a higher rate of false-positive findings and would mean confronting people who are not actually affected by FH with a suspected diagnosis of a serious genetic disease with a markedly increased risk of cardiovascular disease. In particular, the results from Futema 2017 show that the rate of false-positive (FP) findings in the index test very much depends on the choice of threshold. For example, an FP rate of 1% was reported for the overall population for the threshold of 141 mg/dl, whereas this rate was 0.1% for a threshold of 164 mg/dl. The extent to which children who are not affected by FH would "benefit" from being made aware of elevated LDL cholesterol levels as part of lipid screening was not the subject of this report. Whether positive aspects such as any resulting dietary and lifestyle changes or negative aspects such as labelling or a possible reduced quality of life would predominate for these children was also not investigated.

When evaluating false-negative findings, it must be borne in mind that these are defined in the studies as a reference test via genetic FH diagnostics, but that ultimately it is not genetics but the lipid profile that is decisive for the therapeutic effect of statins. This may mean that the negative consequences of an overlooked HeFH are less severe than would generally be expected.

The extent to which universal lipid screening (including genetic verification of all suspected cases) would lead to overdiagnosis remains largely unclear. It seems unlikely that screening for abnormal lipid profiles would result in people being diagnosed with FH that, without screening, would not have caused them any problems during their lifetime. This is because, firstly, HeFH-associated cardiovascular morbidity usually occurs before mid-adulthood and, secondly, competing non-cardiovascular deaths before mid-adulthood are relatively rare in Germany. However, as FH is a heterogeneous disease with over 100 genetic variants [24,36] the potential harm caused by overdiagnosis of a universal lipid screening programme is difficult to estimate.

Assessment of the diagnostic consequences of possible FH screening in Germany

Since neither the VRONI nor the Fr1dolin study are expected to provide complete data on diagnostic accuracy and neither of them has yet provided any reliable data on FH prevalence in Germany, only the results of the 2 studies included, Wald 2016 and Futema 2017 (see

Section 4.4) can be used to estimate the consequences of nationwide, universal screening for FH, particularly for the detection of children with HeFH. Assuming an actual HeFH prevalence of 1:300 in children aged between 8 and 10 years (with the option of approved drug therapy) and a sensitivity of 66.7%, a specificity of 100% and a PPV of 100%[4] and assuming 693,000 newborns per year in Germany (as of 2023 [37]) and full participation in screening, screening for FH would have the following consequences: Of a total of 2310 children with actual HeFH, 1540 would be correctly identified due to an LDL-C level above the threshold of 164 mg/dl. These 1540 children could rely on the test result with a PPV of 100% and could immediately start guideline-compliant treatment.

However, due to the low sensitivity of 66.7%, 770 children would have a false-negative result from the index test - the FH in these children would remain undetected. If one assumes the worst case scenario and uses the lower limit (20.8%) of the 95% CI reported in Futema 2017 for sensitivity, only 480 children with FH would be correctly detected by the index test in the present scenario - 1830 children with FH would be incorrectly informed that they were very likely not affected. In the scenario outlined, it is not possible to assess the extent to which this harbours a potential for harm for those with FH that exceeds the possible advantage for individuals correctly classified with FH and the very high specificity.

If - as already described elsewhere - the test threshold were lowered to 130 mg/dl or 135 mg/dl, for example, in order to increase sensitivity, this would in turn lead to an increase in "false alarms", in that children who do not have FH would receive a false-positive result. If this approach were chosen for universal lipid screening for FH, it would have to be ensured that the lipid levels specified would not give rise to any incentives to classify children with hyperlipidaemia of other origins as "ill". However, once the information is available, it will very likely be used to cause anxiety through a large number of additional diagnoses in people who may not need treatment or to justify an intervention - be it nutritional counselling or even drug therapy.

Cascade screening as an alternative option

The alternative to universal lipid screening in childhood or adolescence is not simply not to offer screening. In Germany, there is a generally available option to identify adults with FH in health check-ups. This could be used to find and treat other affected family members - especially children and adolescents. This approach is known as cascade screening [38]. Other potentially affected family members can be approached by the primarily identified index person themselves or supported by organizational measures within the health care system [1,39,40]. Successful cascade screening has been reported in the Netherlands, among other countries [41,42]; this approach is therefore currently being implemented and further

[4] with an LDL-C threshold of 164 mg/dl; Futema 2017, see Section 4.4.4

optimized in many countries [43,44]. In contrast, universal screening is currently only offered in individual countries around the world, e.g. in Slovenia [45].

Compared to universal screening, cascade screening offers the advantage of identifying more severe FH subtypes in particular, because people whose family members are affected by particularly early or particularly severe symptoms are more likely to receive medical care and are therefore accessible to cascade screening without an additional invitation or reminder. In a similar way, treatment would also be focussed on those in particular need of treatment - also thanks to the expected higher adherence. Both points are important due to the heterogeneity of FH subtypes. In addition, an implemented cascade screening system would also enable a flexible response to new findings, e.g. regarding the start of treatment (younger children?) or the intensity of treatment (new treatment options?), as the time of screening is not organizationally linked to the age of the subjects to be screened. A known disadvantage of cascade screening is that people with HeFH are not found if the disease is not known through family members, which would argue in favour of specifically targeting risk groups for health checks. Data protection and autonomy must also be particularly carefully considered in cascade screening [46].

If cascade screening is introduced, an accompanying evaluation should be planned and implemented from the outset (previous projects can provide guidance, see e.g. [47]). To this end, data collection should be embedded in health care, so that it is both complete and linked to long-term follow-up, and focused on the most important outcomes and thus be as cost-effective as possible. In addition to the research questions to be defined for the cascade screening itself, an RCT conducted in an everyday health care setting using this data collection should be planned and embedded as part of the evaluation. This should address the open research question of the optimal time to start statin therapy. The considerations of the European Society of Cardiology (ESC) regarding the implementation of registry-based RCTs should also be taken into account here [48]. An additional comparative observational study for people affected (or their parents) who do not consent to randomization should also be planned and implemented [49,50]. Finally, target group-appropriate information about both the cascade screening itself and the research questions addressed by the accompanying evaluation should be added.

Overall, it would also appear to make more sense from a cost perspective to implement cascade screening (for which a certain amount of evidence is available) with a well thought-out and targeted accompanying evaluation, than universal lipid screening (for which evidence is lacking) with or without an accompanying evaluation.

6 Conclusion

Based on the available evidence, there is no hint of a benefit from universal blood lipid screening for FH in children and adolescents. There are no comparative intervention studies of the screening chain. When comparing earlier with later initiation of treatment (treatment with a fixed, average statin dose), a hint of a benefit can be inferred for earlier initiation. However, the underlying cohort study is not only subject to considerable risk of bias, but also does not allow conclusions to be drawn for universal lipid screening due to the selection of a high-risk population within the population with FH. Appropriate studies of the diagnostic accuracy of measuring blood cholesterol levels against the genetic reference standard are available. With a small number of affected individuals, these indicate a potentially low sensitivity (worst case approximately 20%).

Based on the above results of the cohort study on statin therapy, it can be concluded that the identification of children and adolescents with FH who are at high risk of an early-onset event makes sense in principle, as early initiation of statin therapy can reduce the risk of a cardiovascular event. The introduction of cascade screening, starting with affected family members (especially parents), should therefore be considered, especially as this is how the children in the cohort study were recruited. If cascade screening is introduced, it should be accompanied by a targeted, pragmatic and cost-effective evaluation embedded in the everyday health care setting. This evaluation should include a comparative study conducted in such a setting to address the open research question of the optimal time to start statin therapy. This rapid report outlines the initial considerations for such an accompanying evaluation.

7 References for English extract

Please see full rapid report for full reference list.

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The full report (German version) is published under

https://www.iqwig.de/en/projects/s24-01.html

Appendix A Search strategies

A.1 Searches in bibliographic databases

Search for systematic reviews

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE® ALL 1946 to February 20, 2024

The following filters were adopted:

- Systematic review: Wong [51] – High specificity strategy
- Paediatric study: Leclercq [52] (adapted)

#	Searches
1	exp Dyslipidemias/
2	(dyslipid?emia* or hyperlipid?emia* or hypercholesterol?emia*).ti,ab.
3	or/1-2
4	exp pediatrics/
5	(infan* or newborn* or new-born or perinat* or neonat* or baby or baby* or babies or toddler* or minors or minors* or boy or boys or boyfriend or boyhood or girl* or kid or kids or child or child* or children* or schoolchild* or schoolchild or adolescen* or juvenil* or youth* or teen* or under*age* or pubescen* or pediatric* or paediatric* or peadiatric* or prematur* or preterm*).af.
6	(school child or school child* or school or school*).ti,ab.
7	or/4-6
8	and/3,7
9	Cochrane database of systematic reviews.jn.
10	(search or MEDLINE or systematic review).tw.
11	meta analysis.pt.
12	or/9-11
13	12 not (exp animals/ not humans.sh.)
14	and/8,13
15	14 and (english or german or multilingual or undetermined).lg.
16	limit 15 to yr="2019 -Current"

2. International HTA Database

Search interface: INAHTA

#	Searches
1	„Dyslipidemias“[mhe]
2	(dyslipidemia*OR dyslipidaemia* OR hyperlipidemia* OR hyperlipidaemia* OR hypercholesterolemia* OR hypercholesterolaemia*)[title] OR (dyslipidemia*OR dyslipidaemia* OR hyperlipidemia* OR hyperlipidaemia* OR hypercholesterolemia* OR hypercholesterolaemia*)[abs]
3	#1 OR #2
4	*FROM 2019 TO 2024
5	#3 AND #4

Search for primary studies: comparative intervention studies of the screening chain

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE® 1946 to March 04, 2024

The following filters were adopted:

- RCT: Lefebvre [53] – Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2023 revision)
- Non-RCT: Search filter with best sensitivity for controlled NRS (Ovid MEDLINE, adapted from PubMed) [54]
- Paediatric study: Leclercq [52] (adapted)

#	Searches
1	exp Dyslipidemias/
2	(dyslipid?emi* or hyperlipid?emi* or hypercholesterol?emi*).ti,ab.
3	or/1-2
4	exp pediatrics/
5	(infan* or newborn* or new-born or perinat* or neonat* or baby or baby* or babies or toddler* or minors or minors* or boy or boys or boyfriend or boyhood or girl* or kid or kids or child or child* or children* or schoolchild* or schoolchild or adolescen* or juvenil* or youth* or teen* or under*age* or pubescen* or pediatric* or paediatric* or peadiatric* or prematur* or preterm*).af.
6	(school child or school child* or school or school*).ti,ab.
7	or/4-6
8	Mass Screening/
9	screen*.ti,ab.
10	or/8-9
11	and/3,7,10
12	exp Randomized controlled Trial/
13	controlled clinical trial.pt.
14	(randomized or placebo or randomly or trial or groups).ab.
15	drug therapy.fs.
16	or/12-15
17	exp animals/ not humans.sh.
18	16 not 17
19	exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/
20	((control and (group* or study)) or (time and factors) or program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-up*).mp.
21	or/19-20
22	or/18,21
23	(animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/
24	hi.fs. or case report.mp.
25	or/23-24
26	22 not 25
27	11 and 26
28	27 and (english or german or multilingual or undetermined).lg.
29	28 and 20200305:3000.(dt).

2. Embase

Search interface: Ovid

- Embase 1974 to 2024 March 04

The following filters were adopted:

- RCT: Wong [51] – Strategy minimizing difference between sensitivity and specificity
- Paediatric study: Leclercq [52] (adapted)

#	Searches
1	exp hyperlipidemia/
2	dyslipidemia/
3	*hyperlipoproteinemia type 2/
4	(dyslipid?emi* or hyperlipid?emi* or hypercholesterol?emi*).ti,ab.
5	or/1-4
6	exp pediatrics/
7	(infan* or newborn* or new-born or perinat* or neonat* or baby or baby* or babies or toddler* or minors or minors* or boy or boys or boyfriend or boyhood or girl* or kid or kids or child or child* or children* or schoolchild* or schoolchild or adolescen* or juvenil* or youth* or teen* or under*age* or pubescen* or pediatric* or paediatric* or peadiatric* or prematur* or preterm*).af.
8	(school child or school child* or school or school*).ti,ab.
9	or/6-8
10	screen*.ti,ab.
11	(random* or double-blind*).tw.
12	placebo*.mp.
13	or/11-12
14	and/5,9-10,13
15	14 not medline.cr.
16	15 not (exp animal/ not exp human/)
17	16 not (Conference Abstract or Conference Review or Editorial).pt.
18	17 not ((afrikaans or albanian or arabic or armenian or azerbaijani or basque or belorussian or bosnian or bulgarian or catalan or chinese or croatian or czech or danish or dutch or english or esperanto or estonian or finnish or french or gallegan or georgian or german or greek or hebrew or hindi or hungarian or icelandic or indonesian or irish gaelic or italian or japanese or korean or latvian or lithuanian or macedonian or malay or norwegian or persian or polish or polyglot or portuguese or pushto or romanian or russian or scottish gaelic or serbian or slovak or slovene or spanish or swedish or thai or turkish or ukrainian or urdu or uzbek or vietnamese) not (english or german)).lg.
19	18 and 20200305:3000.(dc).

3. The Cochrane Library

Search interface: Wiley

- Cochrane Central Register of Controlled Trials: Issue 2 of 12, February 2024

The following filter was adopted:

- Paediatric study: Leclercq [52] (adapted)

#	Searches
#1	[mh „Dyslipidemias“]
#2	(dyslipid?emi* or hyperlipid?emi* or hypercholesterol?emi*):ti,ab
#3	#1 or #2
#4	[mh „pediatrics“]
#5	(infan* or newborn* or new-born or perinat* or neonat* or baby or baby* or babies or toddler* or minors or minors* or boy or boys or boyfriend or boyhood or girl* or kid or kids or child or child* or children* or schoolchild* or schoolchild or adolescen* or juvenil* or youth* or teen* or under*age* or pubescen* or pediatric* or paediatric* or peadiatric* or prematur* or preterm*)
#6	(school child or school child* or school or school*):ti,ab
#7	#4 or #5 or #6
#8	[mh „Mass Screening“]
#9	screen*:ti,ab
#10	#8 or #9
#11	#3 and #7 and #10
#12	#11 not (*clinicaltrial*gov* or *trialsearch*who* or *clinicaltrialsregister*eu* or *anzctr*org*au* or *trialregister*nl* or *irct*ir* or isrctn or *controlled*trials*com* or *drks*de*):so
#13	#12 not ((language next (afr or ara or aze or bos or bul or car or cat or chi or cze or dan or dut or es or est or fin or fre or gre or heb or hrv or hun or ice or ira or ita or jpn or ko or kor or lit or nor or peo or per or pol or por or pt or rom or rum or rus or slo or slv or spa or srp or swe or tha or tur or ukr or urd or uzb)) not (language near/2 (en or eng or english or ger or german or mul or unknown))) with Cochrane Library publication date Between Mar 2020 and Mar 2024, in Trials

Search for primary studies: comparative intervention studies on start of treatment

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE® 1946 to March 27, 2024

The following filters were adopted:

- RCT: Lefebvre [53] – Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-and precision maximizing version (2023 revision)

- Non-RCT: Search filter with best sensitivity for controlled NRS (Ovid MEDLINE, adapted from PubMed) [54]
- Paediatric study: Leclercq [52] (adapted)

#	Searches
1	exp Hyperlipoproteinemia Type II/ or Hyperlipidemias/
2	familial hypercholesterol?emia*.ti,ab.
3	or/1-2
4	exp pediatrics/
5	(infan* or newborn* or new-born or perinat* or neonat* or baby or baby* or babies or toddler* or minors or minors* or boy or boys or boyfriend or boyhood or girl* or kid or kids or child or child* or children* or schoolchild* or schoolchild or adolescen* or juvenil* or youth* or teen* or under*age* or pubescen* or pediatric* or paediatric* or peadiatric* or prematur* or preterm*).af.
6	(school child or school child* or school or school*).ti,ab.
7	or/4-6
8	and/3,7
9	exp Randomized controlled Trial/
10	controlled clinical trial.pt.
11	(randomized or placebo or randomly).ab.
12	clinical trials as topic.sh.
13	trial.ti.
14	or/9-13
15	exp animals/ not humans.sh.
16	14 not 15
17	exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/
18	((control and (group* or study)) or (time and factors) or program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-up*).mp.
19	or/17-18
20	or/16,19
21	(animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/
22	hi.fs. or case report.mp.
23	or/21-22
24	20 not 23
25	and/8,24
26	limit 25 to yr="1995 -Current"

2. Embase

Search interface: Ovid

- Embase 1974 to 2024 March 27

The following filters were adopted:

- RCT: Wong [51] – Strategy minimizing difference between sensitivity and specificity
- Paediatric study: Leclercq [52] (adapted)

#	Searches
1	*hypercholesterolemia/
2	*hyperlipidemia/
3	exp „familial hypercholesterolemia“/
4	familial hypercholesterol?emia*.ti,ab.
5	or/1-4
6	exp pediatrics/
7	(infan* or newborn* or new-born or perinat* or neonat* or baby or baby* or babies or toddler* or minors or minors* or boy or boys or boyfriend or boyhood or girl* or kid or kids or child or child* or children* or schoolchild* or schoolchild or adolescen* or juvenil* or youth* or teen* or under*age* or pubescen* or pediatric* or paediatric* or peadiatric* or prematur* or preterm*).af.
8	(school child or school child* or school or school*).ti,ab.
9	or/6-8
10	(random* or double-blind*).tw.
11	placebo*.mp.
12	or/10-11
13	and/5,9,12
14	13 not medline.cr.
15	14 not (exp animal/ not exp human/)
16	15 not (Conference Abstract or Conference Review or Editorial).pt.
17	16 not ((afrikaans or albanian or arabic or armenian or azerbaijani or basque or belorussian or bosnian or bulgarian or catalan or chinese or croatian or czech or danish or dutch or english or esperanto or estonian or finnish or french or gallegan or georgian or german or greek or hebrew or hindi or hungarian or icelandic or indonesian or irish gaelic or italian or japanese or korean or latvian or lithuanian or macedonian or malay or norwegian or persian or polish or polyglot or portuguese or pushto or romanian or russian or scottish gaelic or serbian or slovak or slovene or spanish or swedish or thai or turkish or ukrainian or urdu or uzbek or vietnamese) not (english or german)).lg.
18	limit 17 to yr=“1995 -Current“

3. The Cochrane Library

Search interface: Wiley

- Cochrane Central Register of Controlled Trials: Issue 2 of 12, February 2024

The following filter was adopted:

- Paediatric study: Leclercq [52] (adapted)

#	Searches
#1	[mh ^“Hyperlipidemias“]
#2	[mh „Hyperlipoproteinemia Type II“]
#3	(familial NEXT hypercholesterol?emia*):ti,ab
#4	#1 or #2 OR #3
#5	[mh „pediatrics“]
#6	(infan* or newborn* or new-born or perinat* or neonat* or baby or baby* or babies or toddler* or minors or minors* or boy or boys or boyfriend or boyhood or girl* or kid or kids or child or child* or children* or schoolchild* or schoolchild or adolescen* or juvenil* or youth* or teen* or under*age* or pubescen* or pediatric* or paediatric* or peadiatric* or prematur* or preterm*)
#7	(school child or school child* or school or school*):ti,ab
#8	#5 or #6 or #7
#9	#4 and #8
#10	#9 not (*clinicaltrial*gov* or *trialsearch*who* or *clinicaltrialsregister*eu* or *anzctr*org*au* or *trialregister*nl* or *irct*ir* or isrctn or *controlled*trials*com* or *drks*de*):so
#11	#10 not ((language next (afr or ara or aze or bos or bul or car or cat or chi or cze or dan or dut or es or est or fin or fre or gre or heb or hrv or hun or ice or ira or ita or jpn or ko or kor or lit or nor or peo or per or pol or por or pt or rom or rum or rus or slo or slv or spa or srp or swe or tha or tur or ukr or urd or uzb)) not (language near/2 (en or eng or english or ger or german or mul or unknown))) with Publication Year from 1995 to 2024, in Trials

Search for primary studies: diagnostic accuracy studies

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE® 1946 to April 02, 2024

The following filter was adopted:

- Paediatric study: Leclercq [52] (adapted)

#	Searches
1	exp Dyslipidemias/
2	(dyslipid?emi* or hyperlipid?emi* or hypercholesterol?emi*).ti,ab.
3	or/1-2
4	exp pediatrics/
5	(infan* or newborn* or new-born or perinat* or neonat* or baby or baby* or babies or toddler* or minors or minors* or boy or boys or boyfriend or boyhood or girl* or kid or kids or child or child* or children* or schoolchild* or schoolchild or adolescen* or juvenil* or youth* or teen* or under*age* or pubescen* or pediatric* or paediatric* or peadiatric* or prematur* or preterm*).af.
6	(school child or school child* or school or school*).ti,ab.
7	or/4-6
8	Mass Screening/
9	screen*.ti,ab.
10	or/8-9
11	and/3,7,10
12	11 and 20220511:3000.(dt).

2. Embase

Search interface: Ovid

- Embase 1974 to 2024 April 03

The following filter was adopted:

- Paediatric study: Leclercq [52] (adapted)

#	Searches
1	exp hyperlipidemia/
2	dyslipidemia/
3	*hyperlipoproteinemia type 2/
4	(dyslipid?emi* or hyperlipid?emi* or hypercholesterol?emi*).ti,ab.
5	or/1-4
6	exp pediatrics/
7	(infan* or newborn* or new-born or perinat* or neonat* or baby or baby* or babies or toddler* or minors or minors* or boy or boys or boyfriend or boyhood or girl* or kid or kids or child or child* or children* or schoolchild* or schoolchild or adolescen* or juvenil* or youth* or teen* or under*age* or pubescen* or pediatric* or paediatric* or peadiatric* or prematur* or preterm*).af.
8	(school child or school child* or school or school*).ti,ab.
9	or/6-8
10	screen*.ti,ab.
11	and/4,9-10
12	11 not medline.cr.
13	12 not (exp animal/ not exp human/)
14	13 not (Conference Abstract or Conference Review or Editorial).pt.
15	14 not ((afrikaans or albanian or arabic or armenian or azerbaijani or basque or belorussian or bosnian or bulgarian or catalan or chinese or croatian or czech or danish or dutch or english or esperanto or estonian or finnish or french or gallegan or georgian or german or greek or hebrew or hindi or hungarian or icelandic or indonesian or irish gaelic or italian or japanese or korean or latvian or lithuanian or macedonian or malay or norwegian or persian or polish or polyglot or portuguese or pushto or romanian or russian or scottish gaelic or serbian or slovak or slovene or spanish or swedish or thai or turkish or ukrainian or urdu or uzbek or vietnamese) not (english or german)).lg.
16	15 and 20220511:3000.(dc).

3. The Cochrane Library

Search interface: Wiley

- Cochrane Central Register of Controlled Trials: Issue 3 of 12, March 2024

The following filter was adopted:

- Paediatric study: Leclercq [52] (adapted)

#	Searches
#1	[mh „Dyslipidemias“]
#2	(dyslipid?emi* or hyperlipid?emi* or hypercholesterol?emi*):ti,ab
#3	#1 or #2
#4	[mh „pediatrics“]
#5	(infan* or newborn* or new-born or perinat* or neonat* or baby or baby* or babies or toddler* or minors or minors* or boy or boys or boyfriend or boyhood or girl* or kid or kids or child or child* or children* or schoolchild* or schoolchild or adolescen* or juvenil* or youth* or teen* or under*age* or pubescen* or pediatric* or paediatric* or peadiatric* or prematur* or preterm*)
#6	(school child or school child* or school or school*):ti,ab
#7	#4 or #5 or #6
#8	[mh „Mass Screening“]
#9	screen*:ti,ab
#10	#8 or #9
#11	#3 and #7 and #10
#12	#11 not (*clinicaltrial*gov* or *trialsearch*who* or *clinicaltrialsregister*eu* or *anzctr*org*au* or *trialregister*nl* or *irct*ir* or isrctn or *controlled*trials*com* or *drks*de*):so
#13	#12 not ((language next (afr or ara or aze or bos or bul or car or cat or chi or cze or dan or dut or es or est or fin or fre or gre or heb or hrv or hun or ice or ira or ita or jpn or ko or kor or lit or nor or peo or per or pol or por or pt or rom or rum or rus or slo or slv or spa or srp or swe or tha or tur or ukr or urd or uzb)) not (language near/2 (en or eng or english or ger or german or mul or unknown))) with Cochrane Library publication date Between May 2022 and Mar 2024, in Trials

A.2 Searches in study registries

1. ClinicalTrials.gov

Provider: U.S. National Institutes of Health

- URL: http://www.clinicaltrials.gov
- Type of search: Basic Search

Search strategy
(dyslipidemia OR dyslipidaemia OR hyperlipidemia OR hyperlipidaemia OR hypercholesterolemia OR hypercholesterolaemia) [Condition/Disease] // Age: child (birth - 17)

2. EU Clinical Trials Register

Provider: European Medicines Agency

- URL: https://www.clinicaltrialsregister.eu/ctr-search/search
- Type of search: Basic Search

Search strategy
dyslipidemi* OR dyslipidaemi* OR hyperlipidemi* OR hyperlipidaemi* OR hypercholesterolemi* OR hypercholesterolaemi* // Select Age Range: Under 18

3. Clinical Trials Information System

Provider: European Medicines Agency

- URL: https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en
- Type of search: Basic Search (Contain any of these terms:)

Search strategy
dyslipidemia, dyslipidaemia, hyperlipidemia, hyperlipidaemia, hypercholesterolemia, hypercholesterolaemia

4. International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

- URL: https://trialsearch.who.int
- Type of search: Standard Search

Search strategy
“familial hypercholesterolemia“ OR “familial hypercholesterolaemia“
dyslipidemia OR dyslipidaemia OR hyperlipidemia OR hyperlipidaemia OR hypercholesterolemia OR hypercholesterolaemia // Search for clinical trials in children