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REVIEW
Health policy

Paediatric familial hypercholesterolaemia screening in Europe: public policy background and recommendations

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Familial hypercholesterolaemia (FH) is under-recognized and under-treated in Europe leading to significantly higher risk for premature heart disease in those affected. As treatment beginning early in life is highly effective in preventing heart disease and cost-effective in these patients, screening for FH is crucial. It has therefore now been recognized by the European Commission Public Health Best Practice Portal as an effective strategy. Model programmes exist in Europe to identify young individuals with FH, which are based on cascade screening of first-degree relatives of affected individuals, universal screening for high cholesterol, opportunistic screening of high-risk individuals, or a combination of the above approaches. Recommendations presented herein to improve identification of FH emphasize that every country should have an FH screening programme. These programmes should be adapted from existing strategies to best fit the individual country's healthcare system, governments should provide financial support for these programmes and related care, and further research to optimize care and implementations should be conducted.

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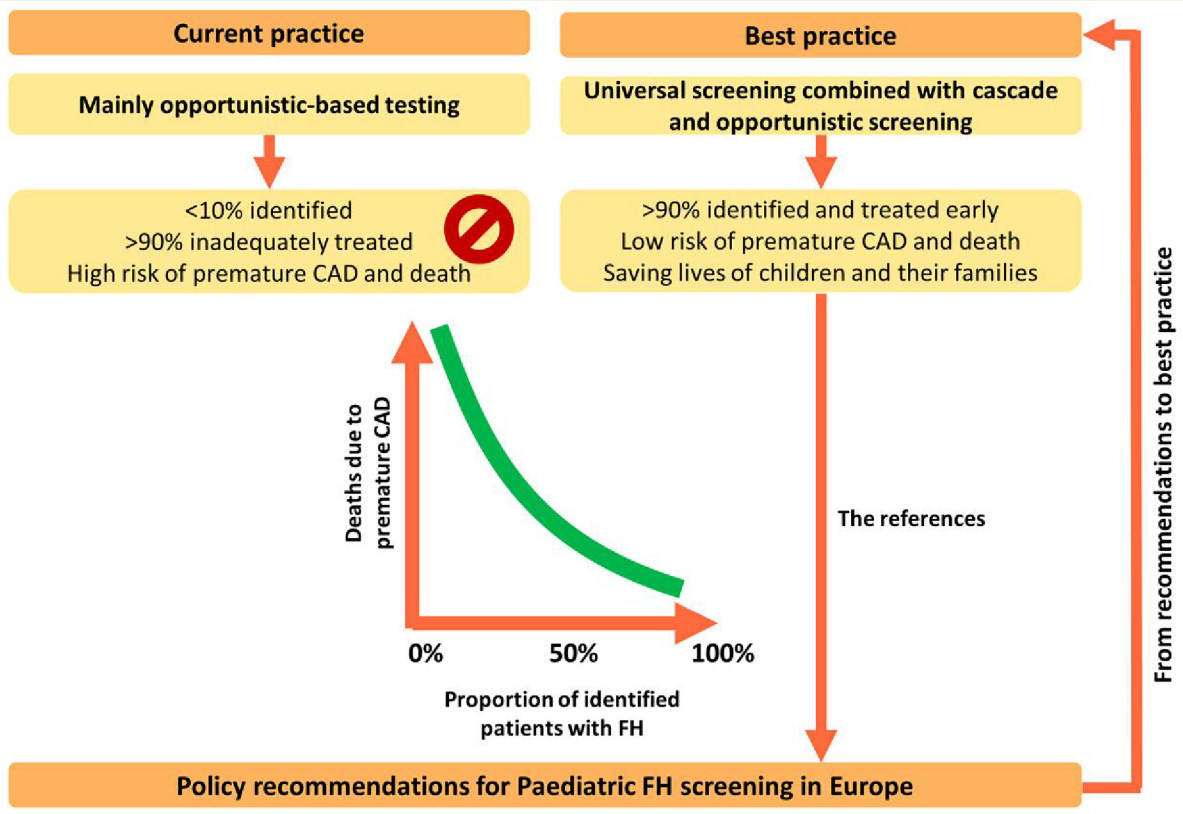
Graphical Abstract



Keywords Cholesterol • Familial hypercholesterolaemia • Myocardial infarction • Preventive cardiology • LDL cholesterol

Familial hypercholesterolaemia

Familial hypercholesterolaemia (FH) is a genetic condition that causes, sustained, lifelong elevation of low-density lipoprotein cholesterol (LDL-C) resulting in premature heart attacks, about half of these occurring before 50 and 60 years of age in men and women, respectively.[1] At any given level of LDL-C, affected persons have three times the risk of a heart attack, because of this lifelong exposure.[2] FH affects 1:311 globally[3–6] and is more common among those with premature cardiovascular disease (CVD; ~1:17).[1,3,4] FH is a genetic disorder with a child of an affected parent having a 50% chance of inheriting the condition. In all of Europe, there are about 500 000 children and 2 000 000 adults; of these, about 2500 have homozygous FH, which is more severe. Early treatment with cholesterol-lowering medication reduces ischaemic heart disease risk; however, <10% of Europeans and <5% of children in Europe have been identified, depriving many of life-saving treatment.[7,8] A global registry, the Familial Hypercholesterolaemia Studies Collaboration published findings on over 42 000 adults from 56 countries[9] : FH is diagnosed late in life (44 years of age), 17% had established CVD at the time of diagnosis, most patients did not achieve current guideline-recommended treatment goals, and patients identified as a result of family screening were younger and less likely to have had heart attacks. Notably, only 2.1% of these adults were diagnosed in childhood.

Lifelong exposure to high LDL-C accelerates the atherosclerotic process. It is known from autopsy studies and natural history studies of children with FH that this process is measurable in those affected, beginning at 8–10 years of age.[1,10] The higher the level of cholesterol and the younger the patient at which cholesterol lowering is started, the greater the benefit.[11] This has been shown in people with FH; when statins were introduced as a treatment in the early 1990s, heart attack rates were reduced by as much as 75%, with the greatest benefit in the youngest people treated.[12] A Dutch study of cholesterol-lowering treatment, beginning in childhood and continued until age 40 years showed that 28% of the affected parents had a heart attack, whereas only 0.5% of their early treated children needed treatment at the same age, and while 7% of the affected parents had died, none of their early treated children had died.[7] This mortality benefit is greater than the benefit shown in treating older adults with advanced atherosclerosis.[13]

FH is diagnosed in children by meeting any of the following criteria: (i) having a positive genetic test for a variant known to cause severe elevation of cholesterol, (ii) having an LDL-C level >190 mg/dL (5 mmol/L) on two occasions, (iii) having a positive family history for FH

accompanied by an LDL-C level >160 mg/dL (4 mmol/L) on two occasions, or (iv) an identified genetic mutation in a parent accompanied by two measurements of LDL-C >130 mg/dL (3.5 mmol/L).[1] In Europe, FH diagnosis occurs almost exclusively by testing children of diagnosed parents. There are very few population-based screening programmes for FH currently underway.

FH is considered a prototype for the application of personalized medicine, defined by the Council of the European Union (EU) in December 2015 as 'a medical model using characterization of individuals' phenotypes and genotypes (e.g. molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention' (https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52015XG1217(01)&from=FR). Personalized medicine relates to the broader concept of patient-centred care, which takes into account that, in general, healthcare systems need to better respond to patient needs. This definition could be applied in a true citizen/patient-centric approach, based on the use of relevant phenotypes and molecular profiling, aiming to identify individuals at risk for FH and CVD, followed by targeted diagnostic, preventive, and innovative therapeutic interventions.

Familial hypercholesterolaemia screening in Europe

FH paediatric screening was recognized in 2021 by the European Commission Public Health Best Practice Portal as one on the best practices in non-communicable disease prevention (https://webgate.ec.europa.eu/dyna/bp-portal/practice.cfm?id=390). Screening for FH is based on measuring cholesterol levels, by performing genetic testing, or a combination. The first organized European screening programmes for FH were based on cascade testing, the genetic testing of at-risk individuals who are first-degree relatives of index cases who test positive for FH. *Table 1* shows existing implemented or pilot FH paediatric screening programmes in European countries. *Figure 1* shows the availability of universal and cascade screening for FH in children and the proportion of children with access to cholesterol and genetic testing for FH in Europe.

The Netherlands

The first organized national screening programme for FH, begun in The Netherlands in 1994, relied upon identification of index cases of genetically confirmed FH patients and then cascade screening of first-degree relatives of index cases, followed by second- and third-degree relatives as more cases were identified.[22] Key elements of this programme were (i) a core group of physicians identifying index patients, (ii) a centralized genetic testing laboratory which confirmed diagnoses, (iii) a centralized group of genetics counsellors and nurses who performed cascade screening of relatives, supporting the index cases and their healthcare providers. This programme became the model for many countries around the world. Key successes of the 20-year programme were the identification of over 30 000 Dutch citizens with FH [including almost 7000 children, assumed to represent over 80% of all FH individuals living in the country (~1:500)], and significant improvements in health outcomes for those with FH, reducing the rate of heart attacks by 75% in those with FH, to the level of the general population, and recognition that FH was twice as frequent in the population as previously thought (~1:250), thus under 50% were identified.[31] For children, the main limitation of the programme was that unless an adult was identified, the child could not be recognized. Given the high frequency of FH, without some element of general population cholesterol screening, all Dutch children with FH could not be identified. Similar programmes have been attempted in Norway, the Czech Republic, Spain, and the UK, though on a smaller scale.

Slovenia

The first attempt worldwide at universal screening of FH began in Slovenia in 1995.[26] Measuring total cholesterol at the age of 5 years was legally mandated as an obligatory part of the blood check-up at the preventive visit with the primary care paediatrician. After a gradual start, systematic efforts to improve its uptake resulted in the programme now reaching ~91% of the population of around 20 000 eligible children each year or 50 newly diagnosed children annually.[27] The universal FH screening programme also enables detection of rare dyslipidaemias as secondary disorders.[32] The programme uses a three-step approach: (i) total non-fasting cholesterol measurement; (ii) children with elevated total cholesterol [>240 mg/dL (6 mmol/L) or >190 mg/dL (5 mmol/L) with positive family history] are referred to paediatric lipid clinic, where a fasting lipid profile is measured and genetic testing performed, if LDL-C levels >140 mg/dL (>3.6 mmol/L); (iii) child–parent cascade screening (of a parent with higher LDL-C level, or both parents if unclear or if homozygous FH, and also siblings; https://world-heart-federation.org/resource/whf-cholesterol-white-paper/). The 'Universal FH screening programme' as a whole [including Steps (ii) and (iii)] was approved by the Slovenian National Council of Paediatrics and by the National Health Council at the Ministry of Health. Regular education about the universal FH screening programme in Slovenia is part of the medical school curriculum and paediatrics residency.

The Czech Republic

In the Czech Republic, opportunistic testing and cascade screening are running, based on the MedPed project (Make Early Diagnoses to Prevent Early Deaths), an international initiative started in 1993 and taken up by >30 countries.[33] MedPed was recognized by the World Health Organization in 1997; the Czech Republic programme began in 1998.[15,34] Since then, a network of 68 lipid centres has been operating across the country and >8800 FH patients, including 647 children have been diagnosed, representing 21% of all FH individuals living in the country. In parallel, selective screening at 5 years of age in children with a positive familial history of premature CVD (<55 years) is mandatory. In 2021, the Czech Republic initiated a pilot project for universal FH screening by lipids from cord blood, with follow-up genetic testing for those with cholesterol above the 85th percentile.

Europe

Early diagnosis is the most urgent need in FH care; without childhood screening, this cannot be accomplished.[1,4,7,9,10,35] It is now recognized that cascade screening alone cannot identify all patients in a given country.[36] In the most successful settings, only about 50% of those with the condition have been identified by cascade screening.

Table 1 Familial hypercholesterolaemia implemented paediatric screening programmes and pilot programmes in Europe

Country	Screening type	Screening setting	Targeted population	Method	FH registry	Reference
Austria	Selective screening combined with cascade screening of siblings	Pilot programme in Vienna	Preschool children from 5 to 7 years with a positive result on a standardized questionnaire	Non-HDL-C and LDL-C for screening, genetic testing	Yes	[14]
	Cascade screening	Nationwide	Children of all ages, adults	TC, LDL-C, genetic testing		N/A
Bulgaria	Cascade screening	Institution-based pilot programme	Children of all ages, adults	LDL-C only	ND	N/A
Czech Republic	Universal screening	Pilot programme	Neonates at birth	TC and LDL-C from the umbilical cord blood; genetic testing (if LDL-C >85th percentile)	Yes	N/A
	Selective screening	Nationwide	Children at 5 and 13 years of age with a positive family history on CVD (<55 years in men and <60 years in women)	TC, LDL-C		N/A
	Cascade screening	Nationwide	Children of all ages, adults	TC, LDL-C, genetic testing		[15]
Denmark	Cascade screening	Nationwide	Children of all ages, adults	TC, LDL-C, genetic testing	Yes	N/A
Estonia	Universal screening	Institution-based pilot programme	Children of all ages, adults	Algorithm screening of HER for LDL-C; followed by genetic testing (in some cases)	ND	[8]
Germany[a]	Universal screening combined with cascade screening	Region-wide pilot programme in Lower Saxony (Programme Fr1dolin)	Children between 2 and 6 years	LDL-C	Yes	[16]
	Universal screening combined with cascade screening	Region-wide pilot programme in Bavaria (The Vroni study)	Children between 5 and 14 years	LDL-C, genetic testing		[17]
Greece	Universal screening combined with cascade screening	Institution-based pilot programme	Children at 3 years	TC and LDL-C, genetic testing	Yes	[8]
Ireland	Cascade screening of first-degree relatives	Nationwide pilot programme	Adults and children above 10 years	Genetic testing if a mutation is identified in a proband; otherwise, TC and LDL-C	Yes	[18]
Italy[b]	Selective screening combined with cascade screening	Nationwide (low attendance rate)	Children with a positive family history of premature CVD or with dyslipidaemia; cascade testing of relatives above 1 year of age	TC, LDL-C for determination of dyslipidaemia; followed by genetic testing	Yes	[19]
Kosovo	Cascade screening	Institution based	Children from infancy, adults	TC, LDL-C, genetic testing	ND	N/A

Continued

Table 1 *Continued*

Country	Screening type	Screening setting	Targeted population	Method	FH registry	Reference
Latvia[c]	Cascade screening	Nationwide pilot programme	Adults above 18 years, rarely children	Mostly LDL-C, rarely genetic testing	Yes	20
Lithuania	Opportunistic testing combined with cascade screening	Institution-based pilot programme	Children and adults up to 85 years	Screening of EHR for LDL-C	Yes	21
Luxembourg	Cascade screening of first-degree family members	Institution-based	Children of all ages, adults	LDL-C in adults; LDL-C and genetic testing in children	ND	N/A
Malta	Cascade screening	Institution-based pilot programme	Adults and children of all ages	LDL-C only	Yes	8
Netherlands	Cascade screening via first-degree relatives until an index-mutation is no longer found in the branches of the family	Nationwide[d]	Children from age 6, adults	Genetic testing, TC, LDL-C	ND	22,23
Norway	Cascade screening of first-degree relatives	Nationwide	Children of all ages, adults	Genetic testing only	Yes	24
Poland	Cascade screening	Institution-based pilot programme	Children (at some institutions), Adults	TC, LDL-C, genetic testing	Yes	8
Portugal	Cascade screening	Nationwide pilot programme (Portuguese FH Study)	Adults and children between 2 and 80 years	TC, LDL-C, genetic testing	No	8,25
Slovakia	Universal screening combined with cascade screening	Nationwide	Children at 11 and 17 years of age	TC for screening; followed by an extended lipid profile at children with high TC	Yes	N/A
	Universal screening combined with genetic testing	Pilot study	Children at 11 years	TC only for screening; genetic testing in parents of children with high TC		N/A
Slovenia	Universal screening combined with cascade screening of parents and siblings	Nationwide (>91% coverage)	Preschool children at 5 years	TC for screening, followed by genetic testing; genetic testing for cascade screening	Yes	26–28
Spain	Cascade screening	Nationwide pilot programme (SAFEHEART: nationwide cohort study of patients with HeFH and their relatives)	Adults and children above 15 years	TC, LDL-C, genetic testing	Yes	N/A
Sweden	Cascade screening of first-degree relatives	Nationwide	Children above 6–8 years, adults	TC, LDL-C, genetic testing	ND	N/A
Switzerland[e]	Cascade screening of family members	Institution based	Any age (1–100 years)	TC, LDL-C, genetic testing	Yes	29
Turkey	Opportunistic testing	Nationwide	High-risk children bellow 1 year old; non-high-risk children between 2 and 7 years or in puberty	LDL-C only for screening	Yes	4

Continued

Table 1 *Continued*

Country	Screening type	Screening setting	Targeted population	Method	FH registry	Reference
Ukraine	Cascade screening	Institution based	Children and adults (between 6 and 60 years)	TC, LDL-C, genetic testing	ND	[8]
United Kingdom	Cascade screening from an index case identified with a genetic variant for FH	Scotland, Wales, and Northern Ireland; not implemented in England	Adults and children above 10 years	TC, LDL-C, genetic testing	Yes	[30]
No systematic paediatric screening of FH implemented						
Albania, Belgium, Bosnia and Herzegovina, Croatia, Finland, France, Hungary, Moldova, Montenegro, North Macedonia, Romania, Russian Federation, Serbia						

The data presented in this table is derived from available publications and a Global FH survey (unpublished data), results of which will be published in full in the near future. The data does not make a distinction between 'cascade screening' and 'cascade testing', instead 'cascade screening' is used for both. Opportunistic testing was not included unless the country used a unique approach.
CVD, cardiovascular disease; EHR, electronic health records; FH, familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; N/A, not available, not applicable; ND, not enough data; Non-HDL-C, non-high-density lipoprotein cholesterol; TC, total cholesterol.
[a]Germany: FH-Alert—Nationwide warning system for informing physicians about FH probability in patients up to 60 years according to their TC and LDL-C.
[b]Italy: LIPIGEN network—A nationwide network for identification and registering patients with FH and other familial dyslipidaemias.
[c]Latvia: Children not included in the national FH registry.
[d]The Netherlands: Twenty years of government funding was stopped in 2014 and was followed by a (temporary) dramatic decline in screening efficiency.
[e]Switzerland: Nationwide screening programme for primary hypercholesterolaemia—SAPPHIRE-FH programme.

Hundreds of thousands of European citizens will remain unidentified, unless universal screening strategies are combined with cascade and opportunistic ones. In the future, the combination of increased cholesterol measurement in children and utilization of digital health technologies may enhance the ability to identify and treat children with FH.

Familial hypercholesterolaemia treatment in childhood

FH treatment recommendations for children are provided by evidence-based guidelines published by the European Society of Cardiology and European Atherosclerosis Society.[1,37] After diet treatment, lipid-lowering medication, primarily statins, should be initiated at 8–10 years of age. The goal of treatment is an LDL-C <135 mg/dL (3.5 mmol/L). Placebo-controlled clinical trials of lipid-lowering drugs have been conducted in children, with durations of 6 months to 2 years, and have been shown to be safe and effective in lowering LDL-C.[38] Treatment should begin at younger ages in more severely affected children. It has been estimated that the number of FH children needed to be treated to prevent one heart attack is <2.[10] An algorithm for paediatric FH care has been developed by the European Atherosclerosis Society.[1] Identified children should receive a consultation by specialized lipid clinics with expertise in paediatric FH.

Treatment of FH in childhood has been documented by several collaborative studies and reports from individual countries. In a report from specialized lipid clinics in eight different countries across Europe, funded by the International Atherosclerosis Society, with age at diagnosis varying from 3 to 11 years, the per cent getting guideline-recommended treatment ranged from 56 to 99%. Treatment goal was not achieved in 23% of those on medication and 66% of those not receiving a statin.[39] About 90% of these children were identified by cascade screening.[39] In Spain and Norway, where national registries exist to monitor care, about two-thirds of eligible children receive treatment and about 40% remain above treatment goal.[40]

Paediatric lipid specialty clinics are present in many European countries, led by paediatricians, endocrinologists, or cardiologists with paediatric training. These centres interact regularly through research and through annual meetings sponsored by the European Atherosclerosis Society. The European Atherosclerosis Society collaboration of specialized lipid centres infrastructure has established uniform standards of diagnosis, management and treatment of patients with lipid disorders[37] and could function similarly to the European Reference Networks, which were successfully implemented in the last decade throughout the EU member states, with aims of providing high-quality, cost-effective, and equitable care to the EU citizens (https://ec.europa.eu/health/ern_en).

Cost analyses of paediatric familial hypercholesterolaemia screening and care

All analyses of the cost-effectiveness of FH care in identified patients demonstrate the value of FH care.[41–43] Controversy regarding FH care from a cost standpoint depends on the cost of screening. The majority of cost analyses are modelled on cascade testing, that is the value of identifying new cases based on this screening strategy, and secondarily, on whether lipid screening vs. genetic testing is more cost-effective. The value of cascade screening and subsequent care for FH in affected children was modelled in Australia,[44] where cascade screening to identify children with FH was cost saving; examination of alternative models showed over 50% were cost saving and all others were highly cost-effective.

A review of the Dutch experience with cascade screening showed multiple benefits of the cascade screening programme

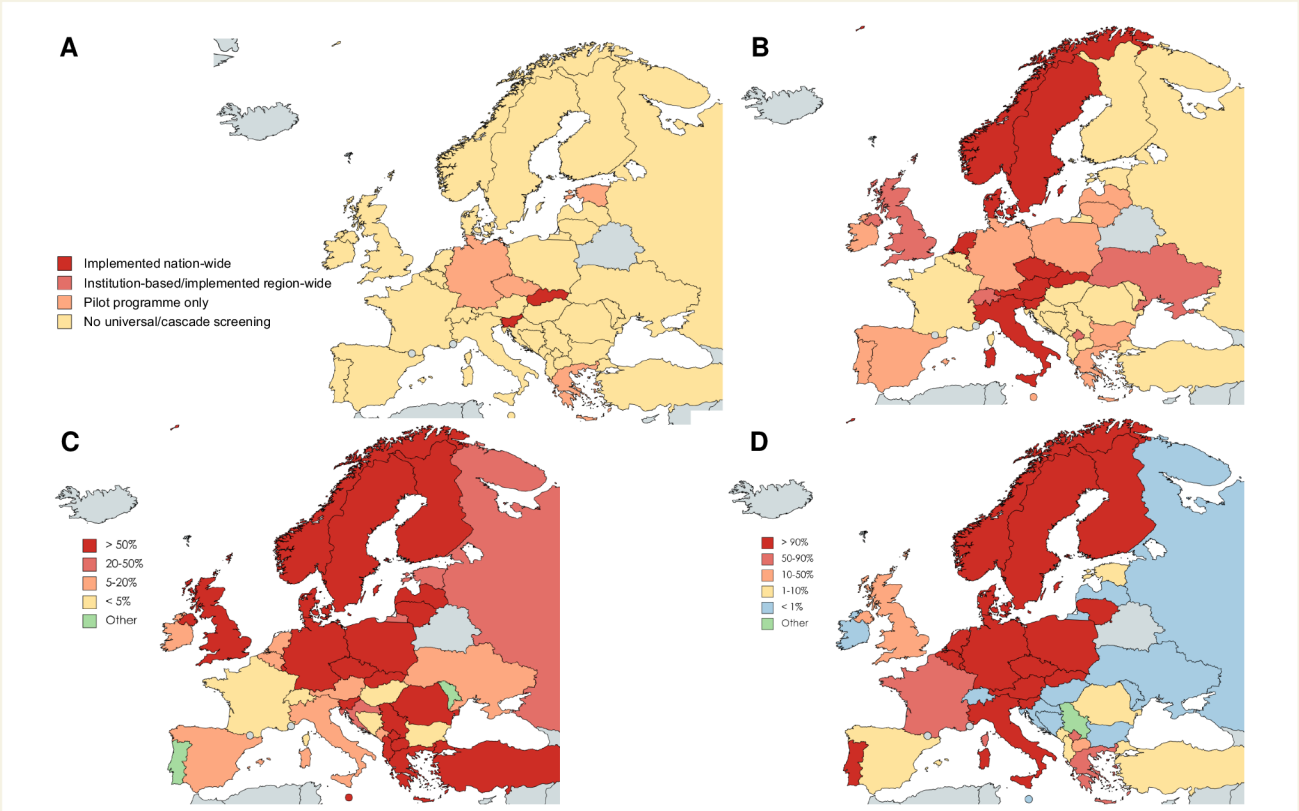


Figure 1 Map of European countries with paediatric screening programmes. (*A*) Availability of universal screening for familial hypercholesterolaemia; (*B*) availability of cascade screening for familial hypercholesterolaemia; (*C*) proportion of children with access to guideline-recommended cholesterol testing; (*D*) proportion of children with access to guideline-recommended genetic testing for familial hypercholesterolaemia. Note that Subsections A and B have the same legend. Maps were created with MapChart.net.

(www.leefh.nl). About 11 healthy life-years are added to each person identified. Cost-effectiveness analyses showed the programme was actually cost saving. Healthcare costs for an unidentified patient are about 12 000 euros higher than for an identified and properly treated patient. The incremental cost-effectiveness ratio for FH cascade screening was less than colon, cervical, and breast cancer screening programmes.

In the UK, a novel model based on universal screening of 1- to 2-year-old children using LDL-C testing, followed by genetic testing for FH in the children, and then reverse cascade testing of parents to identify undiagnosed adults was found to be cost-effective compared with traditional methods of FH identification.[45] This approach has several advantages in that it identifies all children via universal screening, it identifies a large number of young, untreated adults (parents) who would also benefit from treatment, and is acceptable to families as it occurs in the context of regular paediatric preventive care.

Patient perspective

Effective implementation of efforts like FH paediatric screening will rely heavily on patient and citizen engagement to inform sound policy. Surveys, focus groups, individual face-to-face interviews, and other opinion-gathering methods to gain first-hand feedback from patients should be performed. Available data suggest patients and families were highly supportive of paediatric screening, commenting on the frequency of late diagnosis in their families, often after a heart attack had occurred.[46–48] The value of genetic confirmation includes knowing a cause for high cholesterol existed that the high cholesterol was not related to behaviour, and that effective treatment was available. Concerns about implementing screening related to guilt regarding genetic transmission, possible inability to obtain life insurance or other societal stigmatization, and difficulty in convincing some relatives to obtain testing.

Evidence gaps and limitations

While the results of meta-analyses, observational data in well-studied cohorts and modelling studies are consistent and conclusive regarding the benefits of early reduction in LDL-C levels on CVD prevention, clinical trials demonstrating this fact have not occurred.[10,11,49,50] There are serious constraints on conducting such trials including the ethics of withholding treatment (which is likely to be beneficial), cost, and the long-time horizon needed to conduct such a trial with clinical events as endpoints. There are concerns about undiscovered long-term unintended effects of taking a lipid-lowering medication for decades. Though harm from cholesterol testing has not occurred, some citizens may not want to participate in such a programme, for example 9% of children do not participate in the Slovenian

programme.[26] Patient concerns include stigmatization related to genetic testing or loss of life insurance benefits.

Policy recommendations

As a result of the information presented above, the following policy recommendations, to be implemented at the country level across Europe are proposed[35]:

(1) Every European country should have an FH early detection screening, diagnosis, and care programme focused on childhood identification and treatment.
   (a) The programme should be aligned with the European Commission Public Health Best Practice Portal for FH.
   (b) There should be country-wide lipid referral centres that coordinate screening and promote family-based care supplemented by regional paediatric lipid centres as needed.
   (c) Lipid referral centres should be guided by the experience of European Reference Networks and the European Atherosclerosis Society Lipid Clinics Network.
(2) The screening programme
   (a) should incorporate cascade, universal, and opportunistic strategies;
   (b) may be based on cholesterol testing, FH genetic testing, or, ideally, a combination of both; and
   (c) should be country specific and could occur in the context of regular healthcare visits (vaccinations), in community settings, or around the perinatal period.
(3) Government healthcare budgets and policies should support.
   (a) FH education for both citizens and healthcare providers.
   (b) Medical care and genetic testing for FH.
   (c) Investment in uptake of relevant best practice models from other countries.
   (d) Reduction in healthcare disparities, including those related to genetic diagnosis.
   (e) Help overcome the information technology divide across European countries.
(4) Research to support childhood FH identification should include:
   (a) Registries that document FH care, monitor progress in achieving guideline-based treatment goals, and measure health outcomes. These should occur in the context of the European Health Data Space and the European Reference network.
   (b) Long-term clinical trials (3–5 years) in children to further assess health outcomes, complications, and cost.
   (c) Implementation science to facilitate guideline-based FH care and assess citizen satisfaction with programmes.
   (d) Personalized medicine strategies to optimize care.

Conclusions

Familial hypercholesterolaemia paediatric screening to prevent heart attacks later in life, both by measurement of cholesterol and genetic testing, has to be seen an important citizen right for all European and beyond. Reviewing scientific data, patient perspectives, and evidence-based medical guidelines, paediatric FH screening should be made available, throughout the EU and wider Europe. This initiative should be encouraged in a time, when there is unprecedented focus on health cooperation at the European level, in the wake of the COVID-19 crisis, with the creation of a new 'European Health Union' (https://ec.europa.eu/info/strategy/priorities-2019-2024/promoting-our-european-way-life/european-health-union_en). This comprises, inter alia, a major new funding programme called 'EU4Health' (https://ec.europa.eu/health/funding/eu4health_en), new European health research partnerships, such as the Innovative Health Initiative (https://www.imi.europa.eu/sites/default/files/uploads/documents/About-IMI/IHI/IHI_SRIA_DraftJune2021.pdf), and significant funding for countries to recover from the COVID-19 Pandemic (https://ec.europa.eu/info/business-economy-euro/recovery-coronavirus/recovery-and-resilience-facility_en). Among these conditions enhancing risk is FH; during the pandemic excess CVD events and mortality occurred in those with the condition, likely enhanced by under-recognition, delayed diagnosis, and delayed or insufficient treatment.[3,9]

A technical meeting on paediatric FH screening under the Slovenian EU Presidency, on 11 October 2021, brought together policy makers and the FH community to shed further light on this issue. Given the presence of a European Commission Public Health Best Practices portal related to childhood screening for FH, and existing models for screening programmes present in some European countries, the time is now ripe for a new policy commitment towards extending systematic FH screening, by cholesterol measurement and genetic testing, across Europe.[4,35] A follow-up meeting of during the Czech EU presidency is scheduled for September 2022. The World Heart Federation Cholesterol Roadmap will provide implementation strategies. Paediatric FH screening, and subsequent guideline-based treatment, can dramatically improve health outcomes for patients with FH, saving and improving young people's lives, and reducing financial and human burdens related to preventable CVD (Graphical abstract).

Author contributions

S.S.G.: conceptualization, investigation, writing—original draft; A.W.: investigation, writing—original draft; U.G.: investigation, writing—original draft, visualization; T.F.: investigation, writing—original draft; N.P.: investigation, writing—original draft; K.I.D.: investigation, writing—original draft; M.D.: investigation, writing—original draft; N.B.: investigation, writing—original draft; J.S.: investigation, writing—original draft; K.K.R.: investigation, writing—original draft; R.D.S.: investigation, writing—original draft; M.H.: investigation, writing—original draft; L.T.: investigation, writing—original draft; I.G.-I.: investigation, writing—original draft; F.J.P.: investigation, writing—original draft; M.G.: investigation, writing—original draft.

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Data availability

Data are available upon request from the corresponding author.

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