Familial hypercholesterolaemia in children and adolescents from 48 countries: a cross-sectional study

*European Atherosclerosis Society Familial Hypercholesterolaemia Studies Collaboration**

Summary

Background Approximately 450 000 children are born with familial hypercholesterolaemia worldwide every year, yet only 2·1% of adults with familial hypercholesterolaemia were diagnosed before age 18 years via current diagnostic approaches, which are derived from observations in adults. We aimed to characterise children and adolescents with heterozygous familial hypercholesterolaemia (HeFH) and understand current approaches to the identification and management of familial hypercholesterolaemia to inform future public health strategies.

Methods For this cross-sectional study, we assessed children and adolescents younger than 18 years with a clinical or genetic diagnosis of HeFH at the time of entry into the Familial Hypercholesterolaemia Studies Collaboration (FHSC) registry between Oct 1, 2015, and Jan 31, 2021. Data in the registry were collected from 55 regional or national registries in 48 countries. Diagnoses relying on self-reported history of familial hypercholesterolaemia and suspected secondary hypercholesterolaemia were excluded from the registry; people with untreated LDL cholesterol (LDL-C) of at least 13·0 mmol/L were excluded from this study. Data were assessed overall and by WHO region, World Bank country income status, age, diagnostic criteria, and index-case status. The main outcome of this study was to assess current identification and management of children and adolescents with familial hypercholesterolaemia.

Findings Of 63 093 individuals in the FHSC registry, 11 848 (18·8%) were children or adolescents younger than 18 years with HeFH and were included in this study; 5756 (50·2%) of 11 476 included individuals were female and 5720 (49·8%) were male. Sex data were missing for 372 (3·1%) of 11 848 individuals. Median age at registry entry was 9·6 years (IQR 5·8–13·2). 10 099 (89·9%) of 11 235 included individuals had a final genetically confirmed diagnosis of familial hypercholesterolaemia and 1136 (10·1%) had a clinical diagnosis. Genetically confirmed diagnosis data or clinical diagnosis data were missing for 613 (5·2%) of 11 848 individuals. Genetic diagnosis was more common in children and adolescents from high-income countries (9427 [92·4%] of 10 202) than in children and adolescents from non-high-income countries (199 [48·0%] of 415). 3414 (31·6%) of 10 804 children or adolescents were index cases. Familial-hypercholesterolaemia-related physical signs, cardiovascular risk factors, and cardiovascular disease were uncommon, but were more common in non-high-income countries. 7557 (72·4%) of 10 428 included children or adolescents were not taking lipid-lowering medication (LLM) and had a median LDL-C of 5·00 mmol/L (IQR 4·05–6·08). Compared with genetic diagnosis, the use of unadapted clinical criteria intended for use in adults and reliant on more extreme phenotypes could result in 50–75% of children and adolescents with familial hypercholesterolaemia not being identified.

Interpretation Clinical characteristics observed in adults with familial hypercholesterolaemia are uncommon in children and adolescents with familial hypercholesterolaemia, hence detection in this age group relies on measurement of LDL-C and genetic confirmation. Where genetic testing is unavailable, increased availability and use of LDL-C measurements in the first few years of life could help reduce the current gap between prevalence and detection, enabling increased use of combination LLM to reach recommended LDL-C targets early in life.

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*Collaboration members are listed in the appendix (pp 4–9)

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See Online for appendix

Introduction

Familial hypercholesterolaemia is a monogenic disorder with a global prevalence of 1 in 311 people, resulting in lifelong increased LDL cholesterol (LDL-C) concentrations and risk of premature atherosclerotic cardiovascular disease (ASCVD).[1,2] In 2021, the European Atherosclerosis Society Familial Hypercholesterolaemia Studies Collaboration (FHSC) reported that adults with familial hypercholesterolaemia were diagnosed between age 40 years and age 49 years, with more than one in six adults already having established ASCVD.[2] However, only 2·1% of adults were diagnosed in childhood or adolescence;[2] hence, undetected familial hypercholesterolaemia might be responsible for one in ten myocardial infarctions under age 50 years.[3] Identification of people with familial hypercholesterolaemia in childhood and early initiation of lipid-lowering medication (LLM) can substantially mitigate the risk of premature ASCVD,

enabling a life course that is equivalent to the general population as opposed to affected parents or grandparents, who are predominantly diagnosed with familial hypercholesterolaemia after an ASCVD event.[2–7] Despite these compelling data, health-care systems worldwide identified less than 10% of individuals of any age with familial hypercholesterolaemia.[1,2] As one child is born with familial hypercholesterolaemia every minute,[8] approaches to early detection should be revised to reduce the deficit between prevalence and detection.

Currently, a quarter of the global population with familial hypercholesterolaemia are estimated to be children or adolescents, offering a unique opportunity to alter the future burden of ASCVD that is attributable to familial hypercholesterolaemia.[9]

We aimed to characterise the child and adolescent population with heterozygous familial hypercholesterolaemia (HeFH) and to provide evidence-based insights that might guide future public health approaches to detecting and managing familial hypercholesterolaemia early in life.

Research in context

Evidence before this study

We conducted a systematic review in OVID and MEDLINE from Jan 1, 2000, to Oct 16, 2022, without language restrictions to ascertain contemporary data and diagnostic and management practices. We used the free and MeSH search terms "familial hypercholesterolaemia", "children", and "adolescents". We also conducted a search of the reference lists of suitable articles. All articles were initially screened by title and abstract for relevance and all that explored familial hypercholesterolaemia in childhood and adolescence and that explored practices for identification, diagnosis, and management of familial hypercholesterolaemia were considered for full-text review. The latest guidelines and practices from consensus statements were also reviewed.

Although there is a consensus among health-care professionals that early identification and management of familial hypercholesterolaemia is imperative for preventing associated cardiovascular disease, early detection, particularly in childhood and adolescence, remains challenging. Current population strategies to identify children with familial hypercholesterolaemia involving case-finding from their parents (ie, cascade testing) have resulted in low rates of identification of familial hypercholesterolaemia in childhood and adolescence. Moreover, the clinical criteria for diagnosis in childhood and adolescence have been extrapolated or adapted from adults, in which diagnoses are intuitively made later in the life course with the likelihood of more extreme phenotypes aiding diagnosis. Increasingly, as public health policies begin to advocate for identifying familial hypercholesterolaemia in childhood and adolescence, understanding the characteristics of children and adolescents with familial hypercholesterolaemia is necessary, as is the use of real-world data to inform current identification and management practices.

Added value of this study

The Familial Hypercholesterolaemia Studies Collaboration is a global registry, to assess identification and management of children and adolescents with familial hypercholesterolaemia. This study included 63 093 individuals with familial hypercholesterolaemia, of whom 11 848 were children or adolescents younger than 18 years from 48 countries.

Most children and adolescents were identified through family cascade testing from an adult relative diagnosed with familial hypercholesterolaemia; thus, children and adolescents are currently not the primary focus of detection strategies. There were differences among country income groups, signifying that identification and diagnosis might be resource dependent. Classic familial-hypercholesterolaemia-related physical signs were uncommon in our cohort, meaning that the identification of familial hypercholesterolaemia in children and adolescents was reliant on LDL cholesterol (LDL-C) measurements and genetic confirmation, but these tests were less common in non-high-income countries. The distribution of LDL-C among children and adolescents with familial hypercholesterolaemia suggests that they are likely to be diagnosed via LDL-C measurements from as early as the first year of life. Our study suggests that initial screening of LDL-C should be followed by genetic testing (where available and accessible) to support diagnosis of children and adolescents with mild phenotypes. Use of clinical criteria without attempts to adapt to children and adolescents will lead to missed diagnoses—particularly in those with a milder phenotype in terms of LDL-C. Among children and adolescents taking lipid-lowering medication (LLM), a larger proportion of boys attained LDL-C targets than girls. Children taking LLM were largely on monotherapy at registry entry and still had high LDL-C concentrations. Increased use of combination therapies might help achieve guideline targets.

Implications of all the available evidence

Treatment and intervention early in life for individuals with familial hypercholesterolaemia can prevent atherosclerotic cardiovascular disease resulting from familial hypercholesterolaemia. However, population efforts are mostly focused on finding adults to enable the subsequent detection of children and adolescents through cascade testing. This notion could be changed through universal screening of children and adolescents, subsequently triggering reverse cascade testing of parents. Diagnosis, in the absence of genetic testing, can be guided by LDL-C from as early as the first year of life. The attainment of recommended LDL-C targets through early and effective management of familial hypercholesterolaemia in children and adolescents will probably require increased doses and use of combination therapies. The combination of these factors might reduce lifetime cardiovascular risk to become similar to people in the general population.

Methods

Study design

For this cross-sectional study, we assessed children and adolescents younger than 18 years with a clinical or genetic diagnosis of HeFH at the time of entry into the FHSC registry between Oct 1, 2015, and Jan 31, 2021. Data in the registry were collected from 55 regional or national registries in 48 countries (appendix pp 26–30).

The FHSC protocol[10] is registered at ClinicalTrials.gov (NCT04272697) and was approved by the Joint Research Compliance Office and Imperial College Research Ethics Committee (Imperial College London, London, UK). Investigators and organisations contributing to the FHSC registry provided written confirmation of compliance with their local research and ethical policies and regulations for sharing data with the FHSC.

FHSC registry data

The FHSC is a multinational network of investigators with access to routinely collected, worldwide data on people with familial hypercholesterolaemia. The FHSC registry collects data on demographic characteristics, clinical variables, laboratory tests, and genetic information. Sex data were collected from electronic health records—the options were male or female. Variables were taken as reported by the treating doctor or the investigator participating in the registry. For type of familial hypercholesterolaemia, diagnosis was made genetically; if genetic data were not available or genetic testing was not done, clinical criteria were used.

Individual-level data from these sources are standardised to a common data dictionary and harmonised to produce a single registry of merged data. If a clinical diagnosis of familial hypercholesterolaemia is made, it is in accordance with established clinical criteria (or modified criteria thereof), such as familial-hypercholesterolaemia criteria of the Dutch Lipid Clinic Network (DLCN); the Simon Broome Diagnostic Criteria for Familial Hypercholesterolemia (Simon Broome); Make Early Diagnosis to Prevent Early Deaths (MEDPED); the Canadian Society of Atherosclerosis, Thrombosis and Vascular Biology; or the Japanese Atherosclerosis Society (JAS).[1,2,10–14] Diagnoses relying on self-reported history of familial hypercholesterolaemia and suspected secondary hypercholesterolaemia are excluded from the registry. People with untreated LDL-C of at least 13·0 mmol/L were excluded from this study as these levels probably signify the presence of homozygous familial hypercholesterolaemia (appendix pp 26–30, 42).[8]

Outcomes

The main outcome of this study was to assess current identification and management of children and adolescents with familial hypercholesterolaemia.

Statistical analysis

Data from the merged dataset were analysed at the individual level. The only exception was the French Registry of Familial Hypercholesterolaemia, as their ethical and research committee did not approve the provision of individual-level data to the FHSC. Here, similar analyses to those conducted on the FHSC merged dataset were conducted by local investigators on their individual-level dataset, and the aggregated results were shared with the FHSC (appendix p 31).

Included data from the FHSC registry were assessed overall (ie, globally) and stratified geographically by WHO region—the South-East Asia and Western Pacific regions were combined due to little data from the South-East Asia region[2]—and country income status via the 2023 World Bank definition of high-income countries and non-high-income countries (appendix p 31).[15] Analyses were also stratified by age (ie, aged ≤9 years or >9 years) as ages younger than 9 years have been recommended for universal screening to identify familial hypercholesterolaemia.[16,17] Analyses grouped by index-case status defined an index case as the first documented person with familial hypercholesterolaemia in a family and defined a non-index case as a relative with familial hypercholesterolaemia who was identified through screening of the family of the index case.

We report descriptive data as median (IQR) for continuous variables; categorical variables are shown as absolute numbers and relative frequencies from the total number of children and adolescents with available data for the corresponding variable. Because of the descriptive nature of our analysis, no attempt was made to account for missing data (appendix p 43). If appropriate, median differences and corresponding 95% CIs were estimated via quantile regression. Kernel density estimation was used to produce probability density functions to show smoothed distributions of non-parametric LDL-C. Smoothed percentile curves were produced by sex and age from generalised additive models for location, scale, and shape and fitted on the data. If appropriate, logistic regression was used to estimate odds ratios (ORs) and 95% CIs for the association between a condition of interest and a specific exposure, adjusting for relevant variables.

The pathway to familial-hypercholesterolaemia diagnosis involves a first-identification stage, whereby children and adolescents are either suspected to have familial hypercholesterolaemia based on clinical criteria or undergo genetic testing as part of family cascade testing (appendix p 32). When clinical criteria were used, most were derived for adult populations and some have been adapted for children and adolescents (eg, Simon Broome or the JAS criteria); others were not (eg, DLCN and MEDPED).[8] We therefore assessed the appropriateness of these criteria for the detection of familial hypercholesterolaemia in children and adolescents by evaluating the distribution of LDL-C concentrations among people with available genetic data and those diagnosed with clinical criteria as a first stage in diagnosis. Clinical criteria were grouped by whether they were adapted or unadapted for children and adolescents.

We also explored LDL-C among children and adolescents without familial hypercholesterolaemia (ie, unaffected relatives of people with familial hypercholesterolaemia or unrelated individuals screened for familial hypercholesterolaemia with negative results) who had been included in the registry. Furthermore, as LDL-C calculated with the Friedewald formula might be affected by changes in triglycerides during childhood and adolescence, we assessed the potential effect of triglycerides on LDL-C concentrations in individuals not taking LLM. Finally, we assessed the proportion of children and adolescents who would be missed (ie, not identified as having familial hypercholesterolaemia when they do have it) if the measured LDL-C cutoffs that had been derived from clinical criteria were applied to those that underwent genetic testing. Thus, we applied the LDL-C cutoffs measured at the 25th and 50th percentiles from DLCN, MEDPED, and Simon Broome.

As the Netherlands contributed a large proportion of data to the overall study population and to the WHO European region, sensitivity analysis excluding the Netherlands was conducted. All analyses were conducted in Stata version 15.1 and R version 3.6.0 was used for smoothed percentile curves.

Role of the funding source

The funders of this study had no role in study design, data collection, data management, data analysis, data interpretation, writing of the report, or the decision to submit for publication.

Results

Of 63 093 individuals in the FHSC registry, 11 848 (18·8%) were younger than 18 years with HeFH (appendix p 42). 10 997 (92·8%) of the 11 848 included individuals were from the European region, of which 5473 (49·8%) were from the Netherlands. Overall, 11 422 (96·4%) individuals were from high-income countries. 10 099 (89·9%) of 11 235 included individuals had a final genetically confirmed diagnosis of familial hypercholesterolaemia and 1136 (10·1%) had a clinical diagnosis. Genetically confirmed diagnosis data or clinical diagnosis data were missing for 613 (5·2%) of 11 848 individuals. Among the 723 clinically diagnosed individuals for whom clinical criteria were known, DLCN was used for 397 (54·9%), MEDPED was used for 246 (34·0%), Simon Broome was used for 58 (8·0%), and other diagnostic criteria were used for 22 (3·0%; appendix pp 25–29). For 233 (20·5%) of 1136 children or adolescents with HeFH, applied clinical criteria were unknown; for 180 (15·8%), a genetic test was conducted but the results were pending at the time of inclusion in the registry. Genetic diagnosis was more common in children and adolescents from high-income countries (9427 [92·4%] of 10 202) than in children and adolescents from non-high-income countries (199 [48·0%] of 415). 3414 (31·6%) of 10 804 children or adolescents were index cases.

Median age at registry entry was 9·6 years (IQR 5·8–13·2); 5756 (50·2%) of 11 476 included individuals were female and 5720 (49·8%) were male (table 1; appendix p 44). Common familial-hypercholesterolaemia-related physical signs were uncommon overall but more prevalent at older ages (table 2; appendix p 33). Cardiovascular risk factors, including hypertension and diabetes, and cardiovascular disease, including coronary artery disease (CAD) or stroke, were infrequent (table 1). Variations in the presence of physical signs and cardiovascular comorbidities were seen by country income groups and geographical regions (table 1; appendix p 34). For example, children and adolescents from non-high-income countries had a higher prevalence of xanthomas (13·6% *vs* 1·8%), and CAD (3·8% *vs* 0·1%) than children and adolescents from high-income countries. Physical signs and cardiovascular comorbidities were generally lower in Europe (appendix p 34). Children and adolescents with CAD had a higher frequency of physical signs and cardiovascular risk factors than children and adolescents without CAD (appendix p 35). Individuals with familial-hypercholesterolaemia-related physical signs had higher frequency of CAD than individuals without these signs (appendix p 36).

At registry entry, 7903 (71·6%) of 11 046 included children or adolescents were not taking LLM and had a median LDL-C of 5·00 mmol/L (IQR 4·05–6·08; table 1). LDL-C among children aged 9 years or younger and in girls were not significantly different (table 2). The LDL-C of children and adolescents not taking LLM in those from non-high-income countries compared with those from high-income countries and among individuals who were index cases were also not significantly different (tables 1, 2). Variables that were associated with a reduced or increased likelihood of having a severe LDL-C phenotype (defined as LDL-C ≥7·8 mmol/L when not taking LLM)[18] are shown in the appendix (pp 37, 45–46).

Median LDL-C concentration was highest at age 2–3 years for both sexes when not taking LLM (5·97 mmol/L [IQR 5·04–6·90] overall, 5·66 mmol/L [4·89–6·75] for male individuals, and 6·10 mmol/L [5·30–7·09] for female individuals; figure 1; appendix p 38). Similar distributions were observed if LDL-C at the time of familial-hypercholesterolaemia diagnosis was considered instead of LDL-C at registry entry; age at diagnosis equalled age at registry entry for 8803 (78·4%) of 11 230 included children and adolescents (appendix pp 39, 48). 1109 (45·4%) of 2442 children and adolescents who were taking LLM had LDL-C below 4·16 mmol/L. Stratification by age (ie, aged <9 years, aged 9 years to <14 years, and aged 14 years to <18 years, to broadly account for puberty) did not reveal any differences in LDL-C beyond the pattern observed when comparing individuals older than 9 years and aged 9 years or younger (appendix p 33). The median LDL-C concentration among 917 children and adolescents without

	Overall cohort	Overall cohort (excluding the Netherlands)	Non-high-income countries*	High-income countries*
Total	11 848	6375	426	11 422
Sex				
Male	5720/11 476 (49·8%)	2921/6003 (48·7%)	198/402 (49·3%)	5522/11 074 (49·9%)
Female	5756/11 476 (50·2%)	3082/6003 (51·3%)	204/402 (50·8%)	5552/11 074 (50·1%)
Missing	372	372	24	348
Age at registry entry, years	9·6 (5·8–13·2)	8·6 (4·8–12·3)	11·0 (7·0–14·0)	9·5 (5·8–13·2)
Age at familial-hypercholesterolaemia diagnosis, years	9·1 (5·3–13·0)	8·0 (4·0–11·8)	10·0 (6·0–13·0)	9·1 (5·3–13·0)
Index case	3414/10 804 (31·6%)	3054/5331 (57·3%)	102/357 (28·6%)	3312/10 447 (31·7%)
Missing	1044	1044	69	975
Corneal arcus	43/4959 (0·9%)	43/4957 (0·9%)	5/228 (2·2%)	38/4731 (0·8%)
Missing	6889	1418	198	6691
Xanthoma	125/5510 (2·3%)	125/5510 (2·3%)	31/228 (13·6%)	94/5282 (1·8%)
Missing	6338	865	198	6140
Hypertension	27/8273 (0·3%)	24/2809 (0·9%)	5/367 (1·4%)	22/7906 (0·3%)
Missing	3575	3566	59	3516
Diabetes	32/8051 (0·4%)	23/2587 (0·9%)	6/326 (1·8%)	26/7725 (0·3%)
Missing	3797	3788	100	3697
Current or past smoker	271/9167 (3·0%)	86/3694 (2·3%)	10/330 (3·0%)	261/8837 (3·0%)
Missing	2681	2681	96	2585
BMI, kg/m²				
Aged 0 years to <5 years	16·7 (15·2–18·1)	17·1 (15·8–18·4)	14·9 (13·6–16·0)	16·7 (15·2–18·1)
Aged 5 years to <10 years	16·0 (14·8–17·6)	16·2 (14·9–18·2)	16·4 (14·4–18·8)	15·9 (14·8–17·6)
Aged 10 years to <15 years	18·6 (16·7–21·1)	19·6 (17·1–22·6)	18·7 (15·3–20·3)	18·6 (16·7–21·1)
Aged 15 years to <18 years	21·1 (19·5–23·5)	22·1 (20·0–25·1)	20·4 (18·1–24·9)	21·1 (19·5–23·4)
Missing	3432	1993	270	3162
Coronary artery disease	27/10 484 (0·3%)	25/5018 (0·5%)	14/368 (3·8%)	13/10 116 (0·1%)
Missing	1364	1357	58	1306
Stroke	2/7484 (<0·1%)	2/2020 (<0·1%)	1/311 (0·3%)	1/7173 (<0·1%)
Missing	4364	4355	115	4249
LLM	3143/11 046 (28·5%)	1207/5573 (21·7%)	185/364 (50·8%)	2958/10 682 (27·7%)
Missing	802	802	62	740
Total cholesterol, mmol/L				
Participants not taking LLM	6·80 (5·75–7·86)	7·20 (6·26–8·20)	7·53 (6·70–9·10)	6·78 (5·70–7·82)
Participants taking LLM	6·00 (5·09–7·07)	6·50 (5·30–7·68)	6·10 (5·23–7·30)	6·00 (5·08–7·06)
Missing	2508	245	48	2408
LDL-cholesterol, mmol/L				
Participants not taking LLM	5·00 (4·05–6·08)	5·38 (4·42–6·39)	5·79 (4·80–7·19)	4·99 (4·01–6·05)
Participants taking LLM	4·35 (3·44–5·34)	4·62 (3·59–5·72)	4·40 (3·40–5·53)	4·34 (3·44–5·33)
Missing	2683	241	48	2616
HDL-cholesterol, mmol/L				
Participants not taking LLM	1·31 (1·10–1·55)	1·40 (1·20–1·60)	1·30 (1·10–1·53)	1·31 (1·10–1·55)
Participants taking LLM	1·19 (1·00–1·40)	1·32 (1·10–1·58)	1·20 (1·00–1·46)	1·19 (1·00–1·40)
Missing	2640	360	61	2533
Triglycerides, mmol/L				
Participants not taking LLM	0·87 (0·63–1·22)	0·80 (0·62–1·12)	0·92 (0·64–1·30)	0·87 (0·63–1·22)
Participants taking LLM	0·87 (0·62–1·23)	0·84 (0·64–1·13)	0·94 (0·70–1·32)	0·86 (0·61–1·22)
Missing	4213	1891	67	4083

Data are n, n/N (%), or median (IQR). Data that were available for included variables are shown in the appendix (pp 20–21). LLM=lipid-lowering medication. *Countries are classified by income status according to the World Bank definition of 2023 (appendix p 20).

Table 1: **Characteristics of children and adolescents with familial hypercholesterolaemia overall and stratified by country income status**

	Children and adolescents stratified by age group		Children and adolescents stratified by sex		Children and adolescents stratified by diagnostic method*		Children and adolescents stratified by index-case status	
	Age ≤9 years	Age >9 years	Male	Female	Clinical diagnosis	Genetic diagnosis	Index case	Not an index case
Total	5495	6348	5720	5756	1136	10 099	3414	7390
Sex								
Male	2626/5319 (49·4%)	3093/6152 (50·3%)	NA	NA	433/901 (48·1%)	5027/9962 (50·5%)	1661/3412 (48·7%)	3727/7333 (50·8%)
Female	2693/5319 (50·6%)	3059/6152 (49·7%)	NA	NA	468/901 (51·9%)	4935/9962 (49·5%)	1751/3412 (51·3%)	3606/7333 (49·2%)
Missing	176	196	NA	NA	235	137	2	57
Age at registry entry, years	5·5 (3·0–7·3)	13·0 (11·0–15·3)	9·7 (5·7–13·1)	9·6 (5·9–13·4)	10·3 (7·0–14·0)	9·5 (5·6–13·4)	6·8 (4·0–11·0)	10·5 (7·0–14·0)
Age at familial-hypercholesterolaemia diagnosis, years	5·3 (3·0–7·4)	12·8 (10·7–15·1)	9·2 (5·2–13·0)	9·0 (5·4–13·0)	8·0 (5·0–12·0)	9·3 (5·3–13·1)	7·0 (3·0–11·0)	10·0 (6·6–13·8)
Index case	2144/5039 (42·6%)	1270/5765 (22·0%)	1661/5388 (30·8%)	1751/5357 (32·7%)	279/765 (36·5%)	2668/9457 (28·2%)	NA	NA
Missing	456	583	332	399	371	642	NA	NA
Corneal arcus	15/2597 (0·6%)	28/2357 (1·2%)	25/2258 (1·1%)	17/2355 (0·7%)	11/915 (1·2%)	29/3649 (0·8%)	15/2373 (0·6%)	21/1650 (1·3%)
Missing	2898	3991	3462	3401	221	6450	1041	5740
Xanthoma	37/3074 (1·2%)	88/2436 (3·6%)	54/2511 (2·2%)	61/2651 (2·3%)	33/1007 (3·3%)	84/3942 (2·1%)	42/2833 (1·5%)	66/1703 (3·9%)
Missing	2421	3912	3209	3105	129	6157	581	5687
Hypertension	9/3316 (0·3%)	19/4992 (0·4%)	13/4141 (0·3%)	12/4104 (0·3%)	19/729 (2·6%)	8/7310 (0·1%)	7/1289 (0·5%)	12/6577 (0·2%)
Missing	2179	1356	1579	1652	407	2789	2125	813
Diabetes	15/3222 (0·5%)	17/4829 (0·4%)	14/4048 (0·4%)	17/3975 (0·4%)	14/696 (2·0%)	17/7179 (0·2%)	7/1166 (0·6%)	17/6485 (0·3%)
Missing	2273	1519	1672	1781	440	2920	2248	905
Current or past smoker	7/4086 (0·2%)	264/5081 (5·2%)	129/4577 (2·8%)	139/4562 (3·1%)	22/716 (3·1%)	242/8272 (2·9%)	14/1910 (0·7%)	225/6644 (3·4%)
Missing	1409	1267	1143	1194	420	1827	1504	746
BMI, kg/m²								
Aged 0 years to <5 years	16·6 (15·2–18·1)	..	16·5 (15·1–17·9)	16·9 (15·3–18·1)	17·2 (14·5–21·3)	16·7 (15·3–18·1)	17·3 (16·0–18·4)	15·4 (14·3–16·9)
Aged 5 years to <10 years	15·8 (14·6–17·5)	16·6 (15·2–18·6)	16·0 (14·8–17·5)	15·9 (14·7–17·8)	16·8 (15·0–19·5)	15·9 (14·7–14·5)	16·0 (14·9–18·1)	15·9 (14·6–17·4)
Aged 10 years to <15 years	..	18·6 (16·7–21·1)	18·5 (16·7–20·9)	18·7 (16·7–21·3)	19·8 (17·4–22·9)	18·3 (16·6–20·7)	19·6 (17·1–22·8)	18·2 (16·6–20·5)
Aged 15 years to <18 years	..	21·1 (19·5–23·5)	21·1 (19·2–23·4)	21·1 (19·6–23·4)	22·9 (20·0–26·6)	20·9 (19·4–23·1)	21·9 (19·6–25·1)	20·8 (19·4–22·9)
Missing	1482	1875	1498	1460	427	2860	673	1947
Coronary artery disease	8/4321 (0·2%)	19/6158 (0·3%)	17/5042 (0·3%)	9/5097 (0·2%)	12/1064 (1·1%)	14/8818 (0·2%)	5/2256 (0·2%)	10/7220 (0·1%)
Missing	1174	190	678	659	72	1281	1158	170
Stroke	2/3070 (<0·1%)	0/4856 (0·0%)	0/3919 (0·0%)	2/3838 (<0·1%)	2/829 (0·2%)	0/9626 (0·0%)	0/1175 (0·0%)	2/6509 (<0·1%)
Missing	2425	1492	1801	1918	307	473	2239	881
LLM	1146/5046 (22·7%)	1997/6000 (33·3%)	1551/5511 (28·1%)	1580/5491 (28·8%)	318/839 (37·9%)	2764/9626 (28·7%)	323/3190 (10·1%)	2555/7169 (35·6%)
Missing	449	348	209	265	297	473	224	221
Total cholesterol, mmol/L								
Participants not taking LLM	7·07 (6·04–8·07)	6·44 (5·50–7·55)	6·70 (5·63–7·76)	6·91 (5·87–7·94)	7·03 (6·23–8·26)	6·90 (5·82–7·90)	7·20 (6·23–8·20)	6·26 (5·34–7·34)
Participants taking LLM	6·10 (5·26–7·20)	5·93 (4·97–7·02)	5·89 (4·97–6·99)	6·08 (5·18–7·24)	6·31 (5·30–7·40)	5·98 (5·09–7·05)	5·82 (4·91–7·03)	5·82 (4·98–6·81)

(Table 2 continues on next page)

	Children and adolescents stratified by age group		Children and adolescents stratified by sex		Children and adolescents stratified by diagnostic method*		Children and adolescents stratified by index-case status	
	Age ≤9 years	Age >9 years	Male	Female	Clinical diagnosis	Genetic diagnosis	Index case	Not an index case
(Continued from previous page)								
Missing	965	1486	1227	1184	79	2369	386	2031
LDL-cholesterol, mmol/L								
Participants not taking LLM	5·25 (4·30–6·30)	4·70 (3·80–5·78)	4·92 (3·95–6·00)	5·09 (4·14–6·16)	5·17 (4·32–6·40)	5·10 (4·17–6·16)	5·30 (4·37–6·34)	4·63 (3·75–5·67)
Participants taking LLM	4·46 (3·69–5·47)	4·26 (3·34–5·30)	4·23 (3·33–5·27)	4·41 (3·54–5·46)	4·54 (3·74–5·43)	4·36 (3·46–5·34)	3·98 (3·06–5·17)	4·21 (3·39–5·14)
Missing	1085	1579	1333	1259	114	2542	400	2177
HDL-cholesterol, mmol/L								
Participants not taking LLM	1·34 (1·14–1·58)	1·27 (1·04–1·50)	1·29 (1·09–1·53)	1·32 (1·10–1·55)	1·40 (1·19–1·66)	1·30 (1·09–1·50)	1·42 (1·24–1·66)	1·20 (1·00–1·42)
Participants taking LLM	1·15 (0·95–1·38)	1·20 (1·01–1·42)	1·17 (0·99–1·40)	1·21 (1·00–1·40)	1·40 (1·14–1·63)	1·16 (0·97–1·37)	1·37 (1·19–1·60)	1·15 (0·96–1·36)
Missing	1039	1555	1261	1227	130	2446	432	2059
Triglycerides, mmol/L								
Participants not taking LLM	0·80 (0·61–1·15)	0·93 (0·69–1·36)	0·83 (0·60–1·20)	0·90 (0·69–1·24)	0·90 (0·62–1·30)	0·86 (0·63–1·21)	0·79 (0·60–1·06)	0·93 (0·66–1·35)
Participants taking LLM	0·87 (0·61–1·26)	0·87 (0·62–1·21)	0·82 (0·59–1·15)	0·90 (0·67–1·30)	0·80 (0·61–1·12)	0·88 (0·62–1·25)	0·84 (0·64–1·18)	0·88 (0·61–1·25)
Missing	1769	2381	2052	2014	221	3603	1412	2585

Data are n, n/N (%), or median (IQR). Data that were available for included variables are shown in the appendix (p 31). LLM=lipid-lowering medication. NA=not applicable. *Clinical diagnosis is defined here as people who did not undergo any genetic testing and genetic diagnosis is defined here as people who had a positive genetic test as the final diagnosis of familial hypercholesterolaemia (appendix p 32).

Table 2: **Characteristics of children and adolescents with familial hypercholesterolaemia stratified by age, sex, type of diagnosis, and index-case status**

familial hypercholesterolaemia was 3·20 mmol/L (IQR 2·70–3·60); these levels were similar when children and adolescents without familial hypercholesterolaemia were stratified by age tertiles (appendix pp 40, 49–50).

Unlike the pattern observed for LDL-C, age-smoothed and sex-smoothed percentiles curves for triglycerides were mostly flat over time (appendix p 51). Moreover, no correlation between LDL-C and triglyceride concentrations was found when data were stratified by 5-year age intervals (Spearman correlation coefficients ranging from –0·06 for children aged 0 years to <6 years to 0·15 for children aged 15 years to <18 years), with an R^2 of 0·022 or less for each age interval (appendix p 40).

Compared with children and adolescents who had been initially identified as having familial hypercholesterolaemia via genetic testing, those who had been initially identified as having familial hypercholesterolaemia with DLCN or MEDPED clinical criteria had higher median LDL-C concentrations (DLCN 0·88 mmol/L [95% CI 0·66 to 1·11], MEDPED 0·79 mmol/L [0·46 to 1·12], genetic testing 4·34 mmol/L [4·27 to 4·42]). Furthermore, children and adolescents who had been initially identified as having familial hypercholesterolaemia with Simon Broome or JAS clinical criteria had closer median LDL-C concentration to people who were initially identified via genetic testing (Simon Broome 0·16 mmol/L [–0·02 to 0·44], JAS criteria 0·16 mmol/L [–1·23 to 1·55], genetic testing 4·34 mmol/L [4·27 to 4·42]; figure 2A).

The 25th percentile of children and adolescents who had been diagnosed with familial hypercholesterolaemia via DLCN had an LDL-C of 4·34 mmol/L and the 50th percentile had an LDL-C of 5·22 mmol/L. Therefore, if only people with LDL-C concentrations higher than these cutoffs were suspected to have familial hypercholesterolaemia, 50–75% of children and adolescents who had been detected directly through genetic testing would have been missed (figure 2B). Despite the measured LDL-C from Simon Broome being similar to genetic testing (25th percentile 3·56 mmol/L, 50th percentile 4·34 mmol/L), applying the 25th (3·65 mmol/L) to 50th (4·49 mmol/L) percentiles would still have led to 28–55% of children and adolescents who had been genetically diagnosed being missed (figure 2B).

At registry entry, 3143 (28·5%) of 11 046 children and adolescents were taking LLM, which increased with age in both sexes (table 2; appendix pp 33, 52–53). 814 (29·1%) of 2799 children and adolescents were prescribed statins and 154 (5·7%) of 2724 children and adolescents were prescribed ezetimibe (appendix p 40). The proportion of children and adolescents taking statins ranged from 10·0% for those younger than 5 years to 41·0% for those aged 15–18 years (appendix pp 52); the proportion of children and adolescents taking ezetimibe ranged from 4·3% for those younger than 5 years to 7·8% for those aged 15–18 years (appendix p 40). The most common prescribed statins were atorvastatin (43·2%),

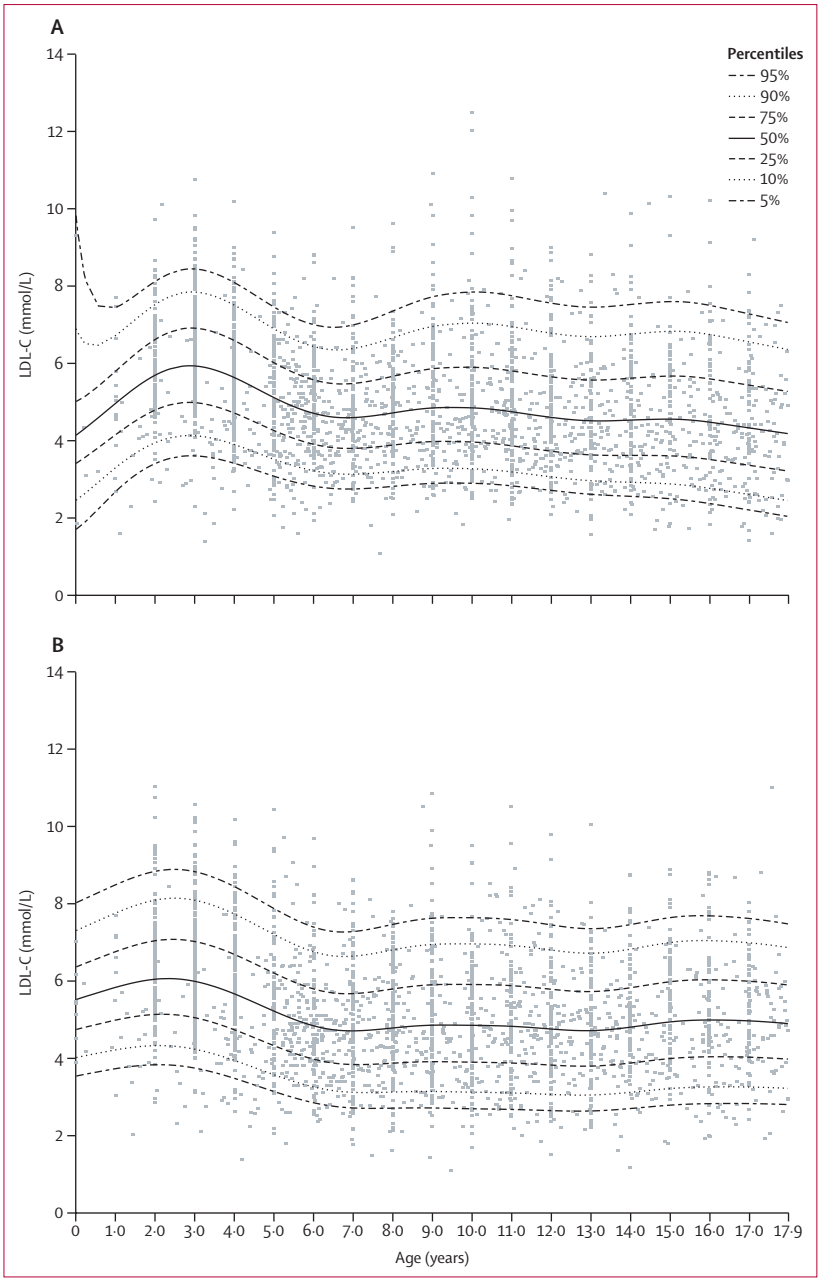


Figure 1: **Smoothed percentile curves for LDL-C concentration at entry into the registry among children and adolescents not taking LLM**

(A) Untreated male individuals. (B) Untreated female individuals. Data are cross-sectional, stratified by age and sex. Equivalent smoothed percentile curves depicting LDL-C in mg/dL instead of mmol/L are available in the appendix (p 47). Smoothed percentile curves of LDL-C of people who were not taking LLM at the time of familial-hypercholesterolaemia diagnosis—for individuals for whom LDL-C at the time of familial-hypercholesterolaemia diagnosis was known—are shown in the appendix (p 48). The number of individuals and median (IQR) LDL-C corresponding to each age are shown in the appendix (pp 38–39). LDL-C=LDL cholesterol. LLM=lipid-lowering medication.

simvastatin (24·4%), and rosuvastatin (18·4%). 10 (0·4%) of 2871 individuals were taking proprotein convertase subtilisin or kexin type 9 inhibitors.

Median LDL-C concentration among children and adolescents with familial hypercholesterolaemia taking LLM was 4·35 mmol/L (IQR 3·44–5·34), compared with 5·00 mmol/L [4·05–6·08] for those not taking LLM (table 1; appendix pp 52–53). Treatment was more common in girls, but did not vary by country income (tables 1, 2). Among those taking statins or ezetimibe, 306 (25·6%) of 1196 male individuals and 250 (20·2%) of 1235 female individuals had LDL-C less than 3·4 mmol/L (figure 3A). After adjusting for age and therapy with statins and ezetimibe, the likelihood of having LDL-C less than 3·4 mmol/L was lower in female individuals than in male individuals (figure 3B; appendix p 41). Compared with monotherapy with statins or ezetimibe, combination therapy (ie, a statin and ezetimibe) was associated with an increased likelihood of having LDL-C less than 3·4 mmol/L (age-adjusted and sex-adjusted OR 1·83, 95% CI 1·19–2·82) compared with no therapy (figure 3B; appendix p 41).

Conducting sensitivity analysis of data from Europe that excluded the Netherlands did not significantly alter the findings (appendix pp 23, 34).

Discussion

Globally, familial hypercholesterolaemia remains under-detected despite being recognised as a public health priority by WHO in 1998.[19] Screening for increased LDL-C concentrations from birth provides the opportunity for early identification and diagnosis of familial hypercholesterolaemia and, through early reductions in LDL-C, cardiovascular health can be preserved.[2,8,19] Our study presents novel findings from the largest dataset of children and adolescents with familial hypercholesterolaemia.

In the FHSC registry, most children and adolescents were not index cases, probably reflecting the use of cascade screening from affected adults to find children with HeFH. This observation is partly affected by the Dutch data, as those data reflect the nationally funded cascade-screening programme (conducted between 1994 and 2014).[5] Compared with adults,[2,8] classic diagnostic criteria (eg, physical signs and premature cardiovascular disease) were uncommon in children and adolescents, and diagnosis was reliant on either LDL-C and genetic confirmation. Distribution of LDL-C concentrations by age suggested that LDL-C concentration could be used to identify people with familial hypercholesterolaemia as early as the first year of life. However, the LDL-C cutoffs that are currently used in different clinical criteria are usually derived from adult populations and need to be adapted to avoid missing potential diagnoses. Once identified, children and adolescents with familial hypercholesterolaemia will require increased use of combination therapies to reach recommended LDL-C targets, similar to adults.

Currently, less than 10% of individuals with familial hypercholesterolaemia worldwide have been identified, with existing diagnosis strategies that are largely dependent on finding adults with familial hypercholesterolaemia first—usually initiated by the occurrence of a premature cardiovascular-disease event in

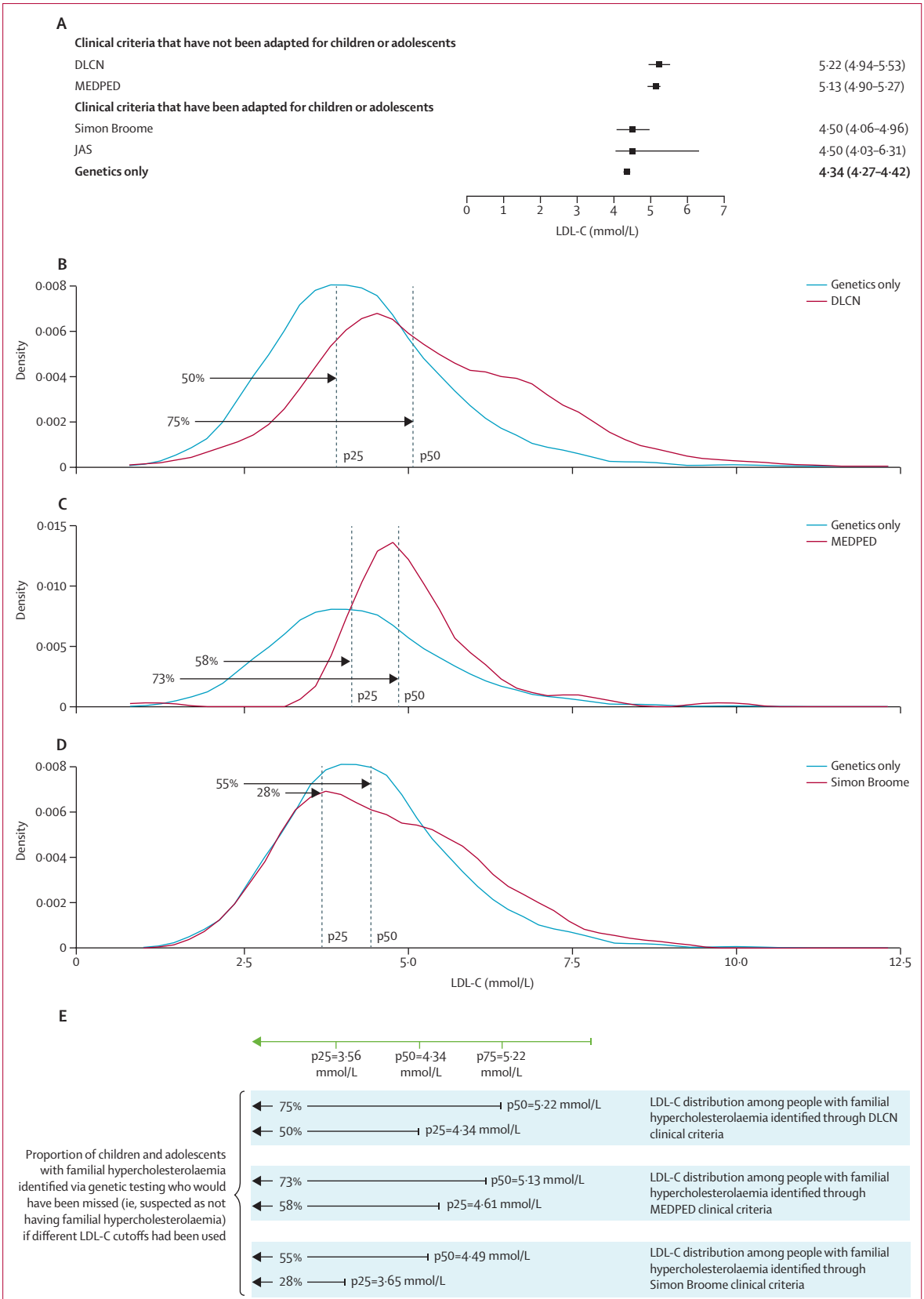


Figure 2: **LDL-C measurements by different diagnostic criteria and the proportion of missed children and adolescents in the genetically tested population via LDL-C cutoffs**
(A) LDL-C (mmol/L) at the time of initial familial-hypercholesterolaemia-detection assessment (appendix p 43) by different diagnostic criteria in children and adolescents among those not taking LLM. Data are median (95% CI).
(B–D) Proportion of children and adolescents not identified as having familial hypercholesterolaemia when they do have it in the genetically tested group not taking LLM at registry entry, if LDL-C at the 25th or 50th percentiles from different clinical criteria were applied to this population group.
(E) Distribution of LDL-C levels among children and adolescents with familial hypercholesterolaemia detected through genetic testing. The green bar represents the LDL-C distribution of children and adolescents who underwent genetic testing only; the horizontal lines represent the distribution of LDL-C for different clinical criteria and are aligned with the percentile measurements of the genetically tested group. DLCN=Dutch Lipid Clinical Network. JAS=Japanese Atherosclerosis Society. LDL-C=LDL cholesterol. LLM=lipid-lowering medication. MEDPED=Make Early Diagnosis to Prevent Early Deaths. Simon Broome=Simon Broome Diagnostic Criteria for Familial Hypercholesterolemia.

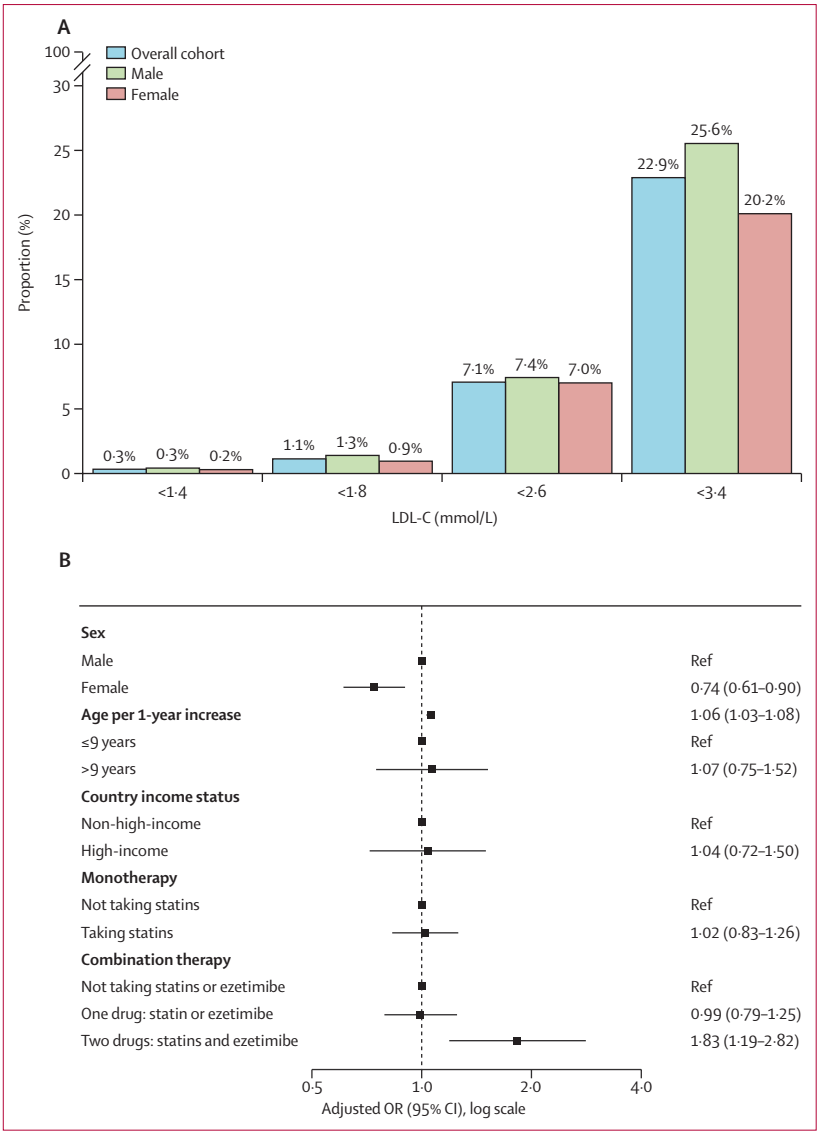


Figure 3: **Children and adolescents taking LLM at registry entry**
(A) Proportion of children and adolescents with LDL-C lower than different thresholds among those taking LLM, overall and by sex. (B) Likelihood of having LDL-C <3·4 mmol/L among children and adolescents taking LLM. Sex is adjusted for age and taking both statins and ezetimibe. Age is adjusted for sex and taking both statins and ezetimibe. Country income status is adjusted for age, sex, and taking both statins and ezetimibe. Monotherapy and combination therapy are adjusted for age and sex. The numbers included in each subgroup with unadjusted and adjusted odds ratios are available in the appendix (p 41). LDL-C=LDL cholesterol. LLM=lipid-lowering medication. OR=odds ratio.

conjunction with increased LDL-C.[2,5–7,19] Thus, children and adolescents are not the primary focus of current detection strategies. These findings support calls to move towards universal screening for familial hypercholesterolaemia in childhood and adolescence.[19–21] There are an estimated 6·4 million children and adolescents with familial hypercholesterolaemia currently.[22] As approximately 450 000 children will be born with familial hypercholesterolaemia every year,[23] and based on the current identification rate (ie, <10%),[2,19] there will be an additional 7·3 million children and adolescents with familial hypercholesterolaemia but who are not identified in 2040. Based on current strategies, only a few of these children and adolescents will be identified as an adult, often if they survive a first cardiovascular event.

As early identification and reductions in LDL-C concentrations can prevent ASCVD, the logical approach to reduce the gap between prevalence and detection is to implement universal screening for familial hypercholesterolaemia in childhood. This approach would be in keeping with the 2020 WHO–UNICEF–*Lancet* Commission, which emphasised the importance of preventive interventions early in childhood rather than corrective actions in adulthood.[24] Furthermore, if children were identified as having familial hypercholesterolaemia in their first decade of life, there would be an opportunity to find affected parents through reverse cascade testing before those adults have had their first cardiovascular event, as the typical age of first parenthood worldwide is 28–34 years.[2,25,26] Child–parent screening has been shown to be feasible and cost-effective through the use of lipid panels.[27–29] However, universal screening can have several challenges. For example, there is variation in the availability and accessibility of resources and governmental support for screening large populations. There is also variation in population education and awareness of the effects of familial hypercholesterolaemia and a need for interventions or genetic counselling, particularly across different resource-limited settings. This variation warrants further research.

Unlike approaches to the detection of familial hypercholesterolaemia in adults, which consider both a personal and family history of ASCVD, physical examination, and LDL-C, approaches to detection in childhood will need to be adapted as physical signs and cardiovascular disease are virtually absent in this age group. Therefore, detection of familial hypercholesterolaemia in childhood will rely upon either LDL-C measurement or the gold-standard method of diagnosis (ie, genetics). However, the implementation of screening strategies at local and national levels by genetic testing or LDL-C testing is far from ubiquitous.[1,2,19,30] Where genetic testing is unavailable or unaffordable, establishing LDL-C cutoffs by age that identify the majority of people who are likely to have a molecular diagnosis of familial hypercholesterolaemia are a practical solution.[30] By comparison with the number of people with familial hypercholesterolaemia, our data had few unselected individuals without familial hypercholesterolaemia, which is not representative of a broad and global general population in childhood.[31] Future work to compare children and adolescents with and without familial hypercholesterolaemia could further inform LDL-C thresholds for screening and diagnosis, which should reflect the characteristics of the region-specific paediatric population.

In our study, the 28·5% of children and adolescents taking LLM might reflect the time from diagnosis, initiating treatment, and registry entry. This understanding

is supported by our observation that children and adolescents from non-high-income countries were more frequently taking LLM at registry entry than children and adolescents from high-income countries. Most guidelines recommend beginning treatment with LLM from age 8 years, as early initiation provides more health gains than treatment initiated later in life.[8,16,19,21,27,32] However, as previously reported by others,[32] we observed that the initiation of statin monotherapy increased after age 10 years. The reasons for this observation are uncertain, but could reflect concerns about the safety of medications at young ages—despite reliable evidence to the contrary,[33–35] with both statins and ezetimibe approved for use in childhood.[8] As with adults, the use of combination therapy was low, with only one in four male individuals and one in five female individuals with familial hypercholesterolaemia in this study having an LDL-C less than 3·4 mmol/L when taking LLM at registry entry; girls had a lower likelihood of reaching current LDL-C recommendations than boys.[2] Nonetheless, LDL-C targets are only one measure of benefit; clinical benefits are observed when treatment is initiated early, despite individuals not reaching target LDL-C.[33] In our study, 45·4% of treated children and adolescents had LDL-C concentrations below the threshold associated with the benefit reported by Luirink and colleagues (ie, mean LDL-C 4·16 mmol/L).[33] As fewer pills might improve adherence to treatment, especially in adolescents, and as combination therapy might not be an option in some countries, aiming for early initiation of therapy with available medications could be an alternative approach.

The limitations of this study warrant consideration. First, sites participating in the study might be clinics with some specialisation in primary dyslipidaemias and factors related to local health-care systems and processes in place to detect people with familial hypercholesterolaemia (eg, care pathways for referral of patients to specialist clinics and any form of screening strategies). These factors might influence the probability of a child or adolescent being included in a registry. However, this factor might also suggest that our results show a better scenario than the one probably happening in paediatric general practice worldwide, in which issues with familial-hypercholesterolaemia detection and management might be more accentuated. Registries reflect real-world practice and are observational, which could account for missing data and some heterogeneity in captured variables, but they also provide valuable information about implementation that is important to inform public health strategies and decision making and have more generalisability than other types of study designs.[36] Second, data from different sources contributing to the FHSC registry (eg, different specialist clinics or identification and diagnosis strategies) might contribute to the potential heterogeneity, although the sources had broadly similar inclusion and exclusion criteria and data were standardised to a common data dictionary.[10] Third, although we statistically adjusted the analysis we cannot fully disregard the presence of potential confounders. For example, we did not adjust for multiplicity of testing within our largely descriptive analysis. Fourth, there were little data from outside the European region. Finally, if a clinical (ie, a non-genetic) diagnosis was made, we cannot disregard that some individuals might have an alternative condition resembling a familial-hypercholesterolaemia phenotype. However, the number of these individuals would be few as other primary dyslipidaemias presenting at a paediatric age are rare diseases; other common ones (eg, polygenic hypercholesterolaemia) present later in life.

Our findings support the implementation of universal screening for familial hypercholesterolaemia in childhood to reduce the widening gap between new cases and detection. In resource-limited settings, universal screening could be achieved through increased access to LDL-C measurements. However, further efforts should be made to increase the accessibility of genetic testing. Once identified, increased use of and improved lifelong adherence to high-intensity statins or combination therapies will be required to ensure that guideline recommendations for LDL-C management are met to preserve the health gains of the detection of familial hypercholesterolaemia early in the life course.

Contributors

All authors revised the manuscript and had final responsibility for the decision to submit for publication. Each author had access to the data from the registry they shared (appendix pp 26–30). The coordinating centre authors had full access to all the data used in this study. Each investigator sharing data with the FHSC was responsible for verifying their data before sharing them. KID, AJV-V, and CATS verified the underlying FHSC registry data for this study. The contributions of individual collaboration members are listed in the appendix (pp 4–9).

Declaration of interests

The competing interests of individual collaboration members are listed in the appendix (pp 11–14).

Data sharing

Data collected in the Familial Hypercholesterolaemia Studies Collaboration (FHSC) registry cannot be shared with third parties due to clauses in data-sharing agreements with data suppliers. Data ownership for the data shared with the FHSC registry remains the property of the data suppliers. The FHSC protocol is available at https://pubmed.ncbi.nlm.nih.gov/27939304/ and the FHSC is registered on ClinicalTrials.gov (NCT04272697).

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