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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See Comment page 6

*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%),

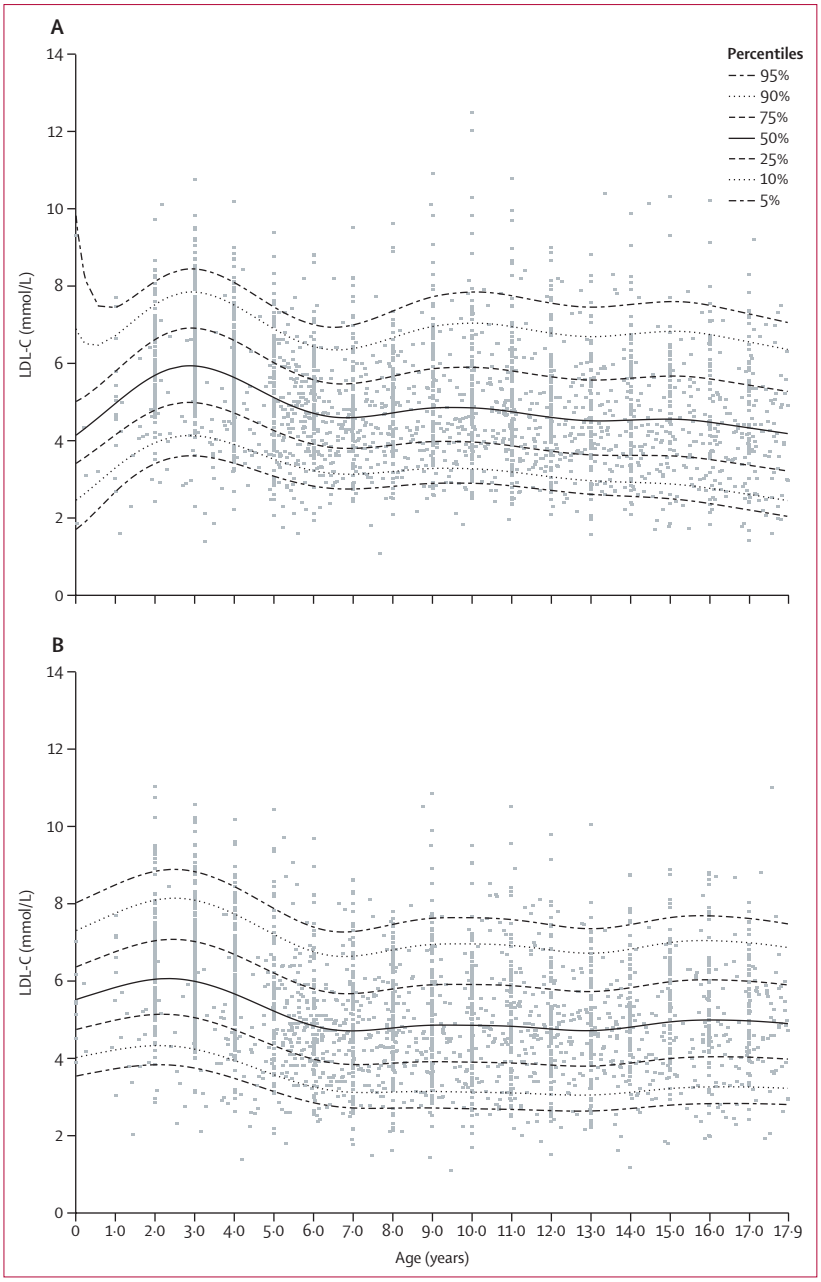

Figure 1: **Smoothed percentile curves for LDL-C concentration at entry into the registry among children and adolescents not taking LLM**

(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

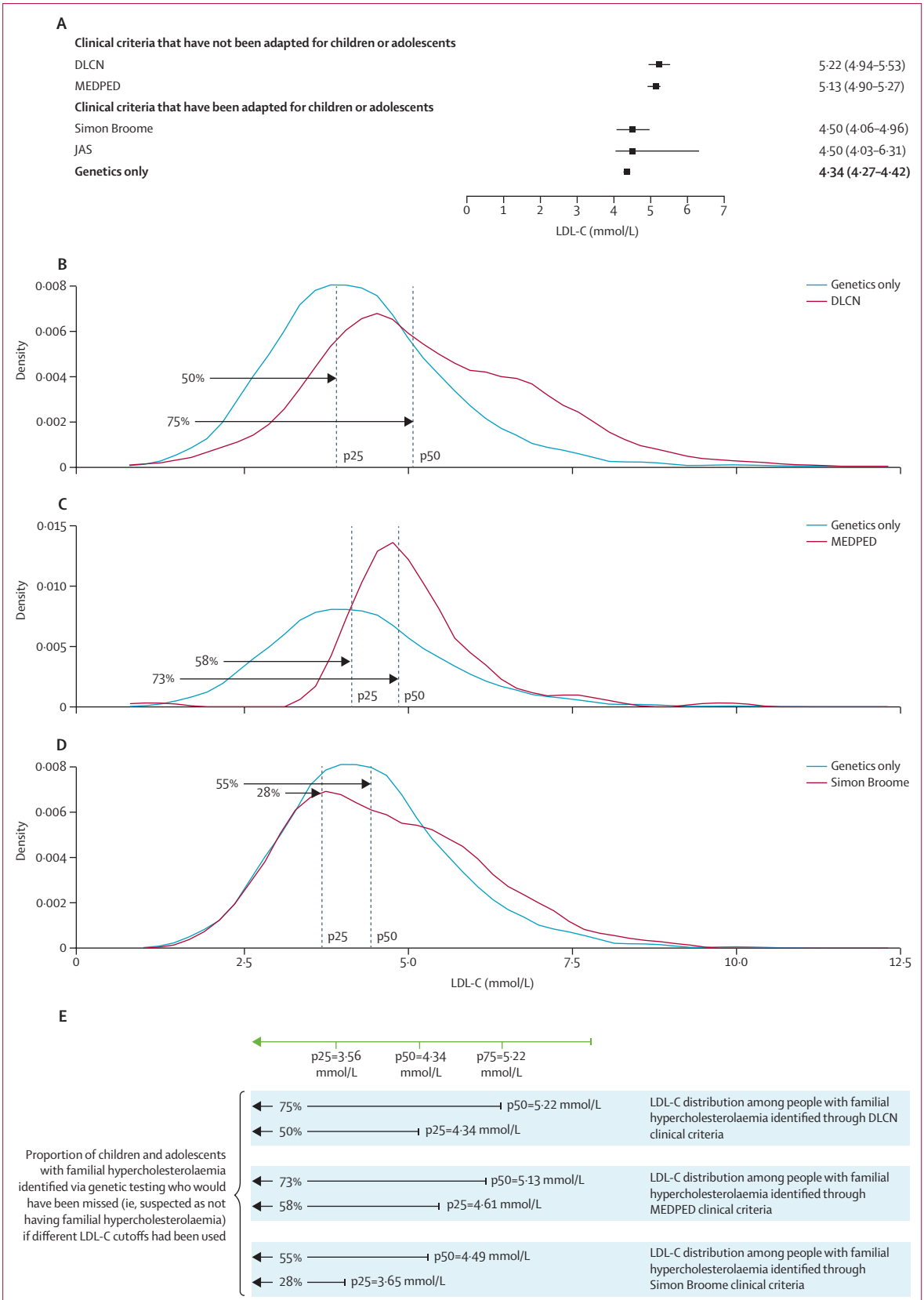

Figure 2: **LDL-C measurements by different diagnostic criteria and the proportion of missed children and adolescents in the genetically tested population via LDL-C cutoffs**
(A) LDL-C (mmol/L) at the time of initial familial-hypercholesterolaemia-detection assessment (appendix p 43) by different diagnostic 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.

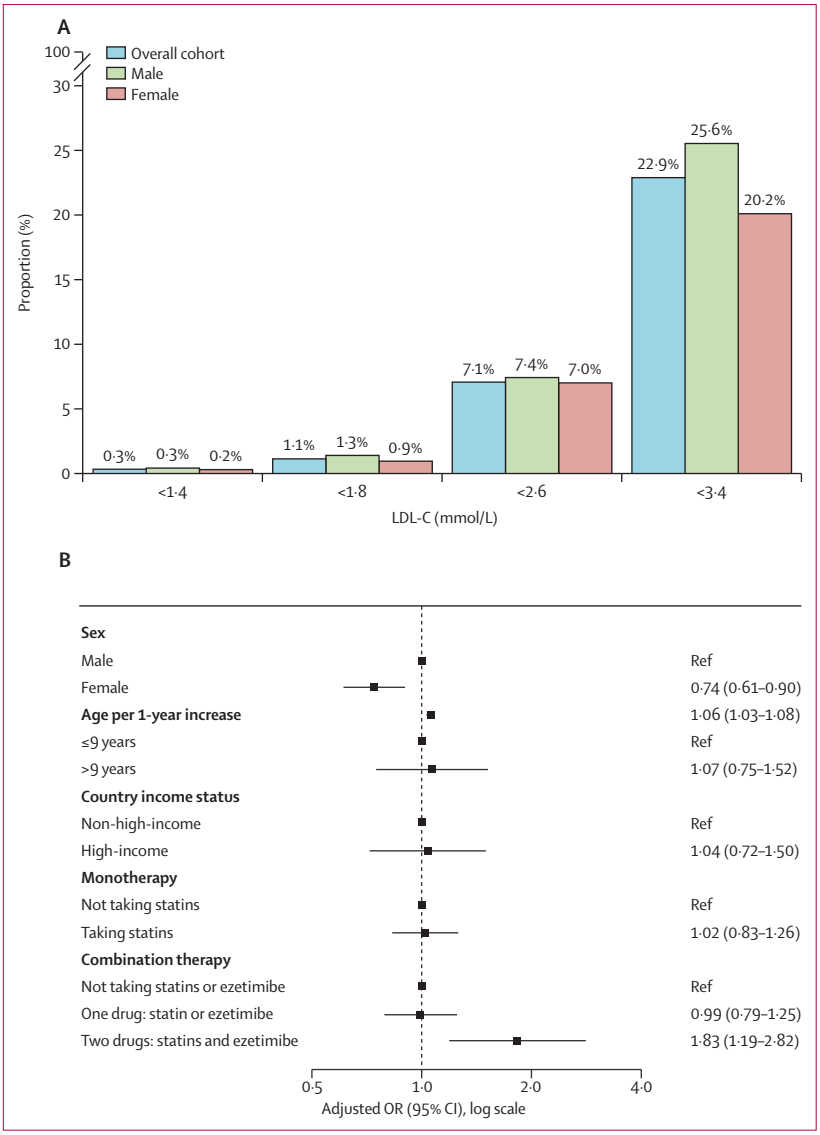

Figure 3: **Children and adolescents taking LLM at registry entry**
(A) Proportion of children and adolescents with LDL-C lower than different thresholds among those taking LLM, overall and by sex. (B) Likelihood of having LDL-C <3·4 mmol/L among children and adolescents taking LLM. Sex is adjusted for 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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References

1 Hu P, Dharmayat KI, Stevens CAT, et al. Prevalence of familial hypercholesterolemia among the general population and patients with atherosclerotic cardiovascular disease: a systematic review and meta-analysis. *Circulation* 2020; **141:** 1742–59.

2 Vallejo-Vaz AJ, Stevens CA, Lyons AR, et al. Global perspective of familial hypercholesterolaemia: a cross-sectional study from the EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC). *Lancet* 2021; **398:** 1713–25.

3 National Organization for Rare Disorders. Familial hypercholesterolemia. 2023. https://rarediseases.org/rare-diseases/familial-hypercholesterolemia/ (accessed Dec 4, 2023).

4 Benito-Vicente A, Alves AC, Etxebarria A, Medeiros AM, Martin C, Bourbon M. The importance of an integrated analysis of clinical, molecular, and functional data for the genetic diagnosis of familial hypercholesterolemia. *Genet Med* 2015; **17:** 980–88.

5 Galema-Boers JM, Versmissen J, Roeters van Lennep HW, Dusault-Wijkstra JE, Williams M, Roeters van Lennep JE. Cascade screening of familial hypercholesterolemia must go on. *Atherosclerosis* 2015; **242:** 415–17.

6 Krogh HW, Mundal L, Holven KB, Retterstøl K. Patients with familial hypercholesterolaemia are characterized by presence of cardiovascular disease at the time of death. *Eur Heart J* 2016; **37:** 1398–405.

7 Hovingh GK, Kastelein JJ. Diagnosis and management of individuals with heterozygous familial hypercholesterolemia: too late and too little. *Circulation* 2016; **134:** 710–12.

8 Wiegman A, Gidding SS, Watts GF, et al. Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. *Eur Heart J* 2015; **36:** 2425–37.

9 The World Bank. Population ages 0–14, total. 2022. https://data.worldbank.org/indicator/SP.POP.0014.TO?end=2020&start=1960&view=chart (accessed Dec 4, 2022).

10 EAS Familial Hypercholesterolaemia Studies Collaboration, Vallejo-Vaz AJ, Akram A, et al. Pooling and expanding registries of FH to assess gaps in care and improve disease management and outcomes: rationale and design of the global EAS FH Studies Collaboration. *Atheroscler Suppl* 2016; **22:** 1–32.

11 Nordestgaard BG, Chapman MJ, Humphries SE, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. *Eur Heart J* 2013; **34:** 3478–90a.

12 Haase A, Goldberg AC. Identification of people with heterozygous familial hypercholesterolemia. *Curr Opin Lipidol* 2012; **23:** 282–89.

13 Ruel I, Brisson D, Aljenedil S, et al. Simplified Canadian definition for familial hypercholesterolemia. *Can J Cardiol* 2018; **34:** 1210–14.

14 Harada-Shiba M, Arai H, Ishigaki Y, et al. Guidelines for diagnosis and treatment of familial hypercholesterolemia 2017. *J Atheroscler Thromb* 2018; **25:** 751–70.

15 The World Bank. World Bank country and lending groups. 2023. https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups (accessed Dec 4, 2023).

16 Wald DS, Bestwick JP, Wald NJ. Child-parent screening for familial hypercholesterolaemia: screening strategy based on a meta-analysis. *BMJ* 2007; **335:** 599.

17 Daniels SR, Gidding SS, de Ferranti SD. Pediatric aspects of familial hypercholesterolemias: recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipidol* 2011; **5** (suppl)**:** S30–37.

18 Santos RD, Gidding SS, Hegele RA, et al. Defining severe familial hypercholesterolaemia and the implications for clinical management: a consensus statement from the International Atherosclerosis Society Severe Familial Hypercholesterolemia Panel. *Lancet Diabetes Endocrinol* 2016; **4:** 850–61.

19 Wilemon KA, Patel J, Aguilar-Salinas C, et al. Reducing the clinical and public health burden of familial hypercholesterolemia: a global call to action. *JAMA Cardiol* 2020; **5:** 217–29.

20 Bedlington N, Abifadel M, Beger B, et al. The time is now: achieving FH paediatric screening across Europe—The Prague Declaration. *GMS Health Innov Technol* 2022; **16:** Doc04.

21 Gidding SS, Wiegman A, Groselj U, et al. Paediatric familial hypercholesterolaemia screening in Europe: public policy background and recommendations. *Eur J Prev Cardiol* 2022; **29:** 2301–11.

22 UN. World population to reach 8 billion on 15 November 2022. https://www.un.org/en/desa/world-population-reach-8-billion-15-november-2022 (accessed Dec 4, 2022).

23 Our World in Data. Births per year. 2022. https://ourworldindata.org/grapher/number-of-births-per-year (accessed Dec 4, 2022).

24 Clark H, Coll-Seck AM, Banerjee A, et al. A future for the world's children? A WHO–UNICEF–*Lancet* Commission. *Lancet* 2020; **395:** 605–58.

25 World Population Review. Average age of having first child by country 2023. https://worldpopulationreview.com/country-rankings/average-age-of-having-first-child-by-country (accessed Nov 24, 2023).

26 Office for National Statistics. Births by parents' characteristics in England and Wales: 2016. 2018. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/livebirths/bulletins/birthsbyparentscharacteristicsinenglandandwales/2016 (accessed Dec 4, 2022).

27 Wald DS, Bestwick JP, Morris JK, Whyte K, Jenkins L, Wald NJ. Child–parent familial hypercholesterolemia screening in primary care. *N Engl J Med* 2016; **375:** 1628–37.

28 McKay AJ, Hogan H, Humphries SE, Marks D, Ray KK, Miners A. Universal screening at age 1-2 years as an adjunct to cascade testing for familial hypercholesterolaemia in the UK: a cost-utility analysis. *Atherosclerosis* 2018; **275:** 434–43.

29 Sustar U, Kordonouri O, Mlinaric M, et al. Universal screening for familial hypercholesterolemia in 2 populations. *Genet Med* 2022; **24:** 2103–11.

30 Ray KK, Ference BA, Séverin T, et al. World Heart Federation cholesterol roadmap 2022. *Glob Heart* 2022; **17:** 75.

31 Balder JW, Lansberg PJ, Hof MH, Wiegman A, Hutten BA, Kuivenhoven JA. Pediatric lipid reference values in the general population: the Dutch lifelines cohort study. *J Clin Lipidol* 2018; **12:** 1208–16.

32 de Ferranti SD, Shrader P, Linton MF, et al. Children with heterozygous familial hypercholesterolemia in the United States: data from the cascade screening for awareness and detection-FH registry. *J Pediatr* 2021; **229:** 70–77.

33 Luirink IK, Wiegman A, Kusters DM, et al. 20-year follow-up of statins in children with familial hypercholesterolemia. *N Engl J Med* 2019; **381:** 1547–56.

34 Rodenburg J, Vissers MN, Wiegman A, et al. Statin treatment in children with familial hypercholesterolemia: the younger, the better. *Circulation* 2007; **116:** 664–68.

35 Vuorio A, Kuoppala J, Kovanen PT, et al. Statins for children with familial hypercholesterolemia. *Cochrane Database Syst Rev* 2019; **2019:** CD006401.

36 Gliklich RE, Dreyer NA, Leavy MB, eds. Registries for evaluating patient outcomes: a user's guide. Rockville, MD, USA: US Agency for Healthcare Research and Quality, 2020.

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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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

SUPPLEMENTARY MATERIAL

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Supplemental Table 1: Characteristics of individual registries at country-level contributing with data to the FHSC at the time of the present analysis

Country (Initials of National Lead Investigators)	Registry Name	Ref.	Registry Inclusion Criteria	Registry Exclusion Criteria	FH Diagnostic Criteria for inclusion	Period of entry shared with FHSC registry	Number of Participants included in the present study
AFRICA							
SOUTH AFRICA (FR, ADM)	…	…	Children/adolescents with a genetic diagnosis of HeFH	Children/adolescents without a genetic diagnosis of HeFH	Clinical signs are unusual in children with HeFH. Although diagnosis of HeFH is based on lipid profiles, genetically confirmed HeFH children were included	2005-2020	139
AMERICAS							
ARGENTINA (PC)	DA VINCI Registry	1	MEDPED	None	MEDPED and genetic diagnosis	2015-2020	8
CANADA (JG)	FH Canada Registry	…	LDL-C > 4.0 mmol/L + Major criterion	metabolic (thyroid, renal, hepatic)	New Canadian FH definition; SBR and DLCN criteria	2014-2017	319
CHILE (RA)	…	…	LDL-C > 160 mg/dL and one of the parents with FH (genetic or LDL > 190 mg/dl).	None	clinical criteria + genetic testing	2014-2020	8
MEXICO (CAAS, AVC)	Registro Mexicano de Hipercolesterolemia Familiar	2	Clinical, biochemical and/or molecular diagnosis, based on MEDPED, Simon Broome and DLCN criteria.	Secondary causes of hypercholesterolemia; did not find affected relatives and whose lipid values overlapped with general population.	Diagnosed by cascade screening through genetic testing of identified mutation in parents.	2017-2021	53
URUGUAY (XR)	GENYCO	…	Index cases have LDL above 155 mg/dl or meet DLCN clinical criteria (they have genetic testing)	No exclusion criteria	Molecular diagnosis of Heterozygous FH	2010-2020	42
VENEZUELA (MMLM)	…	…	DLCN clinical criteria and genetic test	No exclusion criteria	DLCN clinical criteria and genetic test	2020-2022	1
EASTERN MEDITERRANEAN							
IRAN (AS)	…	…	DLCN clinical criteria showing probable or definite diagnosis	DLCN scores not qualifying for probable or definite FH diagnosis	DLCN clinical criteria and Genetic Test	2016-2019	12
IRAQ (MA)	…	…	LDL-C above 160 mg/dl with no secondary cause; with or without skin manifestations	Renal disease, Thyroid disease, Diabetes (any syndrome causing impaired lipid level) by paediatric consultation.	DLCN and LDL-C	2018-2022	1
LEBANON (MA)	…	…	LDL-C level consistent with FH, family history of premature coronary artery disease, and/or baseline high cholesterol in one parent, and/or presence of an FH-causing mutation	Refusal of parents to include their child in the study	MEDPED/WHO criteria diagnosis and the DLCN were used to detect the patient with FH, and confirmed by genetic testing	2016-2021	3
OMAN (KAR)	Oman FH	…	Age ≥2 years	Triglycerides > 5 mmol/L (442 mg/dL). Hypothyroidism. Proteinuria ≥1g/L. Obstructive liver disease. Chronic renal failure. On immunosuppressant or steroids	DLCN and genetic if index case. As part of cascade screening if one parents is the index case	2015-2019	7
PAKISTAN (FS)	Pakistan FH Registry	…	Laboratory Lipid profile, especially LDL value. Xanthomas and/or corneal arcus. Personal and Familial history, if possible	Diabetes and Liver Diseases, if HbA1c and liver enzymes data are available	DLCN. Genetics, if possible. In some cases, LDL cut-offs was used	2019-2020	12
SAUDI ARABIA (FA, KA)	…	…	Diagnosed by genetic testing	None	Genetic testing (NGS)	2015-2021	83
	Gulf Familial Hypercholesterolemia Registry	3	≥2 years of age	Triglycerides > 5 mmol/L (442 mg/dL). Hypothyroidism. Proteinuria ≥1g/L. Obstructive liver disease. Chronic renal failure. On immunosuppressant or steroid	DLCN and genetic if index case. As part of cascade screening if one of the parents is the index case	2012-2017	

Country (Initials of National Lead Investigators)	Registry Name	Ref.	Registry Inclusion Criteria	Registry Exclusion Criteria	FH Diagnostic Criteria for inclusion	Period of entry shared with FHSC registry	Number of Participants included in the present study
EUROPEAN REGION							
AUSTRIA (CB)	FASS DIR EIN HERZ -FH REGISTRY	…	Simon Brome criteria (possible FH) for children <18 years: LDL-C ≥ 160 mg/dL in two assessments after 3 months on a lipid modified diet or LDL-C ≥130 mg/dL in two assessments after 3 months of fat-modified diet if one parent has a genetic defect or + positive family history of early cardiovascular disease and/or high cholesterol levels in one parent	Diabetes mellitus, morbid obesity with obesity related lipid elevation, Thyroid dysfunction if diagnosis was prior to hypercholesterolaemia diagnosis / if no FH related genetic defect could be detected.	Simon-Broome Criteria (possible FH)	2016-2021	143
BELGIUM (OD)	…	…	<18 years	No exclusion criteria	LDL > 130 with either: LDL> 160; or a family history of early CVD (first or second degree); or positive Genetic test	2014-2020	170
BULGARIA (AP)	FH Registry Bulgarian Society of Cardiology	…	DLCN equal or more than 6 points. Majority of included cases are captured by cascade screening	Secondary forms of hypercholesterolemia are excluded based on the examination of HbA1C, thyroid and liver function	DLCN clinical criteria only	2018	4
CROATIA (ZR)	…	…	Patients who are in our outpatient clinic	Those who did not comply with DLCN criteria	DLCN criteria only	2018-2021	1
CYPRUS (AGP)	CyFH	…	A previous diagnosis of FH and/or LDL >160 mg/ dL + Dutch Lipid Clinic Network criteria.	Major systemic disease, patients with a very short life expectancy). Failure to sign consent form	DLCN clinical criteria and LDL-C >160 mg/dL.	2019-2022	1
CZECH REPUBLIC (TF)	...	...	Children identified by a combined strategy of 1) selective screening based on a positive familial history; a) FH diagnosi in first/second degree relatives or b) premature atherothrombotic vascular complications in first/second degree relatives; assessed at age 5 and repeated at age 13; 2) opportunistic screening, i.e. health care-related blood testing; 3) cascade screening; fulfilling MedPed criteria or carrying a familial disease-causing mutation.	Secondary hypercholesterolemia	MEDPED criteria and/or Genetic Test	1998-2018	304
FRANCE (SB)	REFERCHOL	4	1. Patients with a clinical and/or genetic diagnosis of Heterozygous FH. 2. Age <18 years old	Homozygous FH and double and compound heterozygous FH.	1. Genetic diagnostic (heterozygous) 2. Clinical diagnostic: - LDL-C value >130 mg/dL and parents with a genetic mutation - LDL-C value >160 mg/dL and parents with a DLCN value ≥8	2015-2022	618
GERMANY (UL, WM, HS)	CareHigh	…	LDL-C >190 mg/dL without lipid lowering therapy. Total cholesterol >290 mg/dL; Tendon xanthomas; Family history of hypercholesterolemia; Family history of myocardial infarction before the age of 50 in	Cognitive impairment. Acute, non-cardiovascular diseases. Surgery within the last three months (not caused by CVD). Chronic, non-cardiac diseases (e.g. severe chronic kidney disease,	LDL-C >190 mg/dL without lipid lowering therapy. Total cholesterol >290 mg/dL; Tendon xanthomas; Family history of hypercholesterolemia; Family history of myocardial infarction before the age of 50 in	2015-2020	14

Country (Initials of National Lead Investigators)	Registry Name	Ref.	Registry Inclusion Criteria	Registry Exclusion Criteria	FH Diagnostic Criteria for inclusion	Period of entry shared with FHSC registry	Number of Participants included in the present study
			second-degree family; or before the age of 60 in first-degree family	dialysis, severe rheumatic arthritis, malignant disease within the last 5 years	second-degree family; or before the age of 60 in first-degree family		
GREECE (ED, EL, AT)	HELLAS-FH	5-7	LDL-C ≥190 mg/L on 2 successive occasions over 3 months; LDL-C ≥160 mg/dL and family history of premature CVD ± baseline high cholesterol in one parent; LDL-C≥ 130 mg/dL and positive genetic diagnosis in the family	Presence of secondary causes of hyperlipidaemia	The Consensus on Familial Hypercholesterolaemia in Children and Adolescents from the EAS	2016-2022	1371
	…	…	Healthy children, total cholesterol and LDL levels above the 97th centile and with one at least parent with the same biochemistry and/or heart disease	Other disorders that could cause dyslipidaemia and no parent with high cholesterol levels	Dutch and Simon-Broome criteria and genetic test for FH genes	2002-2017	
HUNGARY	FH register	8	DLCN more than 6 points	Informed consent	Initially use DLCN, and genetic testing (NGS)	2016-2022	5
IRELAND (VM)	Irish FH registry	…	LDL above 4mmol/L Parent with FH. Referred to Lipid Clinic	Nephrotic syndrome. Drug induced Hyperlipidaemia	Parents confirmed FH through DLCN. FH Genetic Testing; LDL above 4mmol/L	2019	4
ISRAEL (RD)	…	…	LDL> 160mg/dL		TC and / or LDL-C cut off genetic test		309
ITALY (AC)	The LIPIGEN study	9-10	Any children/adolescents with clinical and/or genetic diagnosis of FH	No exclusion criteria	Clinical and/or genetic diagnosis of FH. Clinical diagnosis per physician judgement considering LDL-C levels and family history	2015-2021	1478
NETHERLANDS (JRVL, ES, GKH)	StOEH	…	Cascade screening performed by the Dutch nationwide screening program. Identification of FH in one of the parents	Unwillingness to participation.	All paediatric FH patients entered in FHSC are diagnosed with a molecular defect resulting in FH	1994-2014	5473
	Erasmus MC Paediatric FH registry	11	Children up to 18 years with genetic FH or clinical criteria (DLCN ≥8)	Homozygous FH	FH pathogenic variant or DLCN criteria with definite FH score ≥8	2014-2018	
NORWAY (KH)	…	…	Medical records of children below 18 years with a diagnosis of heterozygous FH, visiting the Lipid Clinic, Oslo University hospital. Only children with at least one prior visit to the clinic	Not confirmed FH based on the diagnostic criteria. Only one visit to the clinic.	Confirmed pathogenic mutation or children with untreated LDL-C between 5-7 mmol/L on repeat testing and a confirmed FH mutation in a first- or second-degree relative	2014-2016	249
POLAND (MB, KC)	Polish National Register of Familial Hypercholesterolemia	12-14	FH genetic tested positive	FH genetic tested negative	Genetic Test only	2006-2019	100
	PoLA-FH-Registry	…	Children under 18 years old	Not confirmed	DLCN and/or genetic test	2014-2022	
PORTUGAL (MB, DC)	Portuguese FH Study	…	Simon Brome criteria (possible FH) for children but up to 18 years old (and not 16 as described in SB)	Diabetes and thyroid dysfunction if diagnosis was prior to hypercholesterolaemia diagnosis	Simon Broome criteria for children. LDL>155mg/dl or TC>260 mg/dl with a family history of hypercholesterolaemia	2015-2018	62
RUSSIA (MVE, AS)	…	…	DLCN, Simon-Broome. Aged 3-16 years. DLCN and Genetic Test and LDL-C cut-offs > 3.5 mmol/L	Secondary reasons for high cholesterol; secondary dyslipidaemia (diabetes mellitus, hypothyroidism, nephrotic syndrome, anorexia, medications)	Simon-Broome, DLCN and Genetic Test and LDL-C cut-offs > 3.5 mmol/L. Any available data from 1st degree relatives.	2004-2020	106

Country (Initials of National Lead Investigators)	Registry Name	Ref.	Registry Inclusion Criteria	Registry Exclusion Criteria	FH Diagnostic Criteria for inclusion	Period of entry shared with FHSC registry	Number of Participants included in the present study
	RENAISSANCE registry	15-18	Simon-Broome criteria with definite or probable diagnosis. Criteria for the diagnosis of FH in children and adolescents (EAS 2015 consensus). Biochemical criteria of FH for relatives	Patients with triglycerides level more than 4.5 mmol/l are not included in the registry	Simon-Broome criteria for the diagnosis of FH in children and adolescents, Genetic Test if possible	2017-2020	
SERBIA (KL)	…	…	Diagnosis of FH and/or LDL >160 mg/ dL + Dutch Lipid Clinic Network criteria + cascade screening	Secondary causes of hyperlipidaemia	DCLN criteria	2016-2019	1
SLOVAKIA (BV)	MedPed FH Slovakia	19-21	DLCN ≥6 or Simon Broom Criteria	NA	DLCN ≥6 or Simon Broom Criteria	1995-2020	5
SLOVENIA (UG)	National pediatric registry of familial hypercholesterolemia and rare dyslipidemias	…	Universal Slovenian FH screening with cascade screening of siblings. Inclusion criteria for FHSC: positive genetics for FH; positive Simon Broome or MEDPED criteria	Negative genetics and not fulfilling Simon-Broome or MEDPED criteria	Genetic test only or Simon Broome criteria or MEDPED	2002-2020	419
SPAIN (PM)	SafeHeart	…	Cascade genetic screening of an index case with a confirmed genetic diagnosis	No exclusion criteria	Genetic test independently of TC and LDL-C concentrations	2013-2017	110
SWITZERLAND (ARM)	SAPPHIRE	…	Family Member where diagnosis of FH confirmed by genetic tests and/or the SSFH (Swiss Society for FH) criteria (age-adapted FH criteria for children/adolescents including very high LDLC values (twice the average LDLC in the respective age group)	None	Family member where diagnosis of FH has been confirmed by genetic tests and/or the SSFH (Swiss Society for FH) criteria	1987-2019	31
UKRAINE (OM)			Simon Broom Criteria	decompensated hypothyroidism, decompensated diabetes mellitus, corticosteroid therapy	Simon Broom Criteria		15
UNITED KINGDOM (HS)	…	…	Simone Broome criteria	Patient who had genetic testing and result negative were excluded and no longer diagnosed as HeFH	Simone Broome criteria	…	2
UZBEKISTAN (ABS)	…	…	DLCN criteria	Dyslipidaemia but low likelihood of FH according to DLCN criteria; secondary causes of hypercholesterolemia: endocrine disorders (Hypothyroidism), nephrotic syndrome, drugs related	DLCN criteria and Genetic Test	2015-2020	3
South East Asia							
INDIA (TFA)	…	…	Patient with premature (<18 years) CAD. Patient with premature (<18 years) cerebral or peripheral vascular disease. Tendinous xanthomata. LDL-C 155 mg/dL	Hyperlipidaemia: abnormal liver enzymes, renal function, thyroid hormones; No hyperglycaemia or albuminuria	DLCN only	2015-2018	2
THAILAND (WK)	Thai FH Registry	22	12 and <18 years participants with FH diagnosis by: DLCN, Simon Broome Criteria, and MEDPED criteria	Secondary causes of hypercholesterolemia	Either of DLCN clinical criteria, SB or MEDPED criteria	2018-2021	1
Western Pacific							
AUSTRALIA	…	…	FH mutation, screened from families with FH	No exclusion criteria	Genetic Test only	2004-2017	83

Country (Initials of National Lead Investigators)	Registry Name	Ref.	Registry Inclusion Criteria	Registry Exclusion Criteria	FH Diagnostic Criteria for inclusion	Period of entry shared with FHSC registry	Number of Participants included in the present study
(GW)							
CHINA (JL, LW)	…	…	DLCN and ACMG Genetic confirmation of mutant allele at the *LDLR*, *APOB*, *PCSK9*, or *LDLRAP1* gene	DLCN< 8, or ACMG or negative genetic test	DLCN and Genetic Test	2015-2018	29
	…	…	DLCN	Definite liver and kidney dysfunction	DLCN clinical criteria + Genetic Test	2005-2018	
JAPAN (MHS, SY)	…	…	age 2 and <18 years, clinical diagnosis of FH by JAS FH paediatric criteria or a genetic diagnosis of FH	HoFH	JAS paediatric FH criteria; For <15 years: LDL-C≧140 mg/dL, family history of premature CAD or FH and/or genetic test For≧15 years: LDL-C≧180 mg/dL, family history of premature CAD or FH, cutaneous or tendon xanthoma, and/or genetic test	2017-2018	8
	…	23	For <15 years: untreated LDL-C level ≥140mg/dL (if total cholesterol level is ≥220 mg/dL, measure LDL-C); family history of FH or premature CAD (blood relative closer than the two parents) For >15 years: untreated LDL-C ≥180mg/dL; tendon xanthomas or xanthoma tuberosum; family history of FH or premature CAD (within the patient's second-degree relatives)	Secondary hyperlipidemia	For <15 years: untreated LDL-C level ≥140mg/dL (if total cholesterol level is ≥220 mg/dL, measure LDL-C); family history of FH or premature CAD (blood relative closer than the two parents) For >15 years: untreated LDL-C ≥180mg/dL; tendon xanthomas or xanthoma tuberosum; family history of FH or premature CAD (within the patient's second-degree relatives)	2010-2020	
MALAYSIA (HN)	MyHEBAT-FH	…	LDL-C ≥5 mmol/L x2 after healthy Heart diet, or LDL-C ≥4 mmol/L 2x plus family history of premature CAD and/or high cholesterol in parent (untreated), or LDL-C ≥3.5 mmol/L x2 plus parent has genetic diagnosis	Secondary causes of dyslipidaemia (e.g. hypothyroidism, cholestatic liver disease, nephrotic syndrome)	DLCN only; DLCN with genetic confirmation	2006-2019	5
SINGAPORE (TS)	FHCARE Registry	…	Possible or definite FH based on Simon Broome Criteria	Secondary hypercholesterolemia (hypothyroidism, biliary cirrhosis, nephrotic syndrome)	Simon Broome and genetic tests were used.	2015-2020	3
TAIWAN (Province of) (TCS)	TW	…	Parents or siblings with phenotypes of severe hypercholesterolemia: LDL-C ≥190 mg/dL and xanthoma, corneal arcus, or premature CHD	Secondary hyperlipidaemias, such as nephrotic syndrome or hypothyroidism	DLCN and Genetic Test	2017-2018	1
VIETNAM (THT)	VINAFH Registry	24	Children with TC and/or LDL-C cut-offs as "Likely FH" phenotype according to the FH criteria for relatives of FH index-case by Starr and/or FH mutation of LDLR, APOB, PCSK9	Secondary hypercholesterolemia: nephrotic syndrome, hypothyroidism, liver disease	Genetic testing, and/or FH phenotypic criteria of Starr, and/or FH phenotypic criteria of Wiegman	2016-2022	31

Supplemental Table 2: Classification of countries by World Bank Income Status year 2023

Non-High-Income Countries	High-Income Countries
Argentina; Bulgaria; China; India; Iran; Iraq; Lebanon; Mexico; Malaysia; Pakistan; Russia; Serbia; Thailand; Ukraine; Uzbekistan; Venezuela; Vietnam; South Africa	Australia; Austria; Belgium; Canada; Chile; Croatia; Cyprus; Czechia; Germany; France; Greece; Hungary; Ireland; Israel; Italy; Japan; the Netherlands; Norway; Oman; Poland; Portugal; Saudi Arabia; Singapore; Slovakia; Slovenia; Spain; Switzerland; Taiwan; United Kingdom; Uruguay

Supplemental Table 3: Aggregated results for quantitative variables at entry into registry in the France registry (REFERCHOL)

	Age Group		Sex		Diagnostic criteria		Index Case Status	
	≤9 Years	>9 Years	Boys	Girls	Clinical	Genetic	Index Case	Non-Index-Case
Age at registry entry	7·0 (6·0-9·0)	14·0 (12·0-16·0)	12·0 (9·0-15·0)	13·0 (9·0-15·0)	11·0 (8·0-15·0)	13·0 (9·0-15·0)	14·0 (11·0-15·0)	12·0 (9·0-15·0)
Age at FH Diagnosis	6·0 (5·0-8·0)	10·0 (7·0-13·0)	8·0 (6·0-11·0)	9·0 (6·0-13·0)	8·0 (6·0-12·0)	9·0 (6·0-12·0)	10·0 (6·0-14·0)	8·0 (6·0-12·0)
Body Mass Index, (kg/m2)								
0-<5	16·4 (14·4-20·3)		15·9 (14·3-20·3)	16·4 (16·0-21·5)	15·2 (14·3-16·7)	20·3 (16·4-21·5)	17·9 (14·3-21·5)	16·4 (14·4-20·3)
5-<10	15·6 (14·5-16·6)		15·7 (14·5-16·8)	15·4 (14·6-16·5)	15·6 (14·6-16·9)	15·4 (14·4-16·5)	15·9 (14·4-17·6)	15·5 (14·6-16·5)
10-<15		18·0 (16·2-20·7)	18·1 (16·2-20·8)	17·9 (16·3-20·7)	17·6 (15·8-19·1)	18·2 (16·3-20·9)	17·9 (15·8-20·6)	18·0 (16·2-20·8)
15-<18		20·2 (18·6-22·5)	19·4 (17·2-21·6)	20·9 (19·1-23·3)	21·1 (18·0-23·5)	20·2 (18·7-22·1)	19·8 (18·3-21·7)	20·4 (18·7-22·7)
Total cholesterol, mmol/L								
Participants Not on LLM	2·91 (2·63-3·53)	2·83 (2·40-3·17)	2·85 (2·41-3·22)	2·89 (2·57-3·33)	2·96 (2·63-3·54)	2·83 (2·49-3·23)	2·97 (2·61-3·50)	2·86 (2·51-3·24)
Participants On LLM	2·81 (2·33-3·45)	2·26 (2·00-2·59)	2·29 (1·96-2·71)	2·32 (2·09-2·73)	2·40 (2·16-2·82)	2·29 (1·97-2·72)	2·51 (2·03-3·21)	2·29 (2·01-2·64)
LDL-cholesterol, mmol/L								
Participants Not on LLM	2·29 (1·94-2·72)	2·13 (1·70-2·51)	2·17 (1·68-2·55)	2·19 (1·88-2·61)	2·27 (1·90-2·73)	2·14 (1·77-2·54)	2·29 (1·89-2·78)	2·18 (1·81-2·56)
Participants On LLM	2·12 (1·74-2·62)	1·63 (1·36-1·90)	1·64 (1·37-1·96)	1·65 (1·38-2·06)	1·73 (1·44-2·12)	1·64 (1·33-2·00)	1·79 (1·36-2·31)	1·64 (1·37-1·96)
HDL-cholesterol, mmol/L								
Participants Not on LLM	0·54 (0·47-0·62)	0·51 (0·44-0·60)	0·51 (0·45-0·60)	0·54 (0·46-0·63)	0·53 (0·46-0·61)	0·53 (0·45-0·62)	0·53 (0·48-0·59)	0·53 (0·45-0·62)
Participants On LLM	0·54 (0·43-0·60)	0·53 (0·46-0·61)	0·53 (0·45-0·59)	0·54 (0·46-0·62)	0·53 (0·45-0·62)	0·53 (0·47-0·61)	0·56 (0·48-0·68)	0·53 (0·45-0·62)
Triglycerides, mmol/L								
Participants Not on LLM	0·73 (0·59-0·91)	0·68 (0·51-0·94)	0·65 (0·50-0·91)	0·74 (0·59-0·95)	0·76 (0·57-0·99)	0·68 (0·55-0·89)	0·75 (0·63-0·96)	0·70 (0·55-0·94)
Participants On LLM	0·69 (0·53-1·03)	0·62 (0·52-0·90)	0·60 (0·47-0·82)	0·68 (0·57-0·93)	0·69 (0·56-0·91)	0·62 (0·51-0·91)	0·64 (0·53-0·91)	0·62 (0·51-0·91)

Supplemental Table 4: Available data for variables included in the present study

Variables	Data available: absolute number and % respect to overall cohort			
	Individual-level data merged into one FHSC dataset	Aggregated data from France Registry (%)	Both, individual-level data and aggregated data, together	Additional Information
	Overall, N=11,230	Overall, N=618	Overall, N=11,848	
Sex	10,858 (96·7%)	618 (100%)	11476 (96·8%)	
Age at Registry Entry	11,225 (99·9%)	618 (100%)	Presented separately	
Age at FH diagnosis	10,721 (95·5%)	369 (59·7%)	Presented separately	
Index Cases	10,186 (90·7%)	618 (100%)	10804 (91·2%)	
Corneal Arcus	4,566 (40·7%)	393 (63·6%)	4959 (41·9%)	
Xanthoma	5,102 (45·4%)	408 (66·6%)	5510 (46·5%)	
Smoking	8,608 (76·7%)	559 (90·5%)	9167 (77·4%)	
Hypertension	7,705 (68·6%)	568 (91·9%)	8273 (69·8%)	
Diabetes Mellitus	7,484 (66·6%)	567 (91·7%)	8051 (68·0%)	
Body Mass Index	7,905 (70·4%)	511 (82·7%)	8416 (71·0%)	
Coronary Artery Disease	9,866 (87·9%) *	618 (100%)	10484 (88·5%)	(*) Information on Coronary Artery Disease at baseline provided in datasets from countries = ARG; AUS; AUT; BEL; BGR; CAN; CHE; CHL; CHN; CYP; CZE; DEU; ESP; GBR; GRC; HRV; HUN; IND; IRL; IRN; IRQ; ISR; ITA; JPN; LBN; MEX; MYS; NLD; NOR; OMN; POL; PRT; RUS; SAU; SGP; SVK; SVN; THA; TWN; UKR; URY; UZB; VEN; VNM; ZAF
Stroke	7,484 (66·6%) *	Not available		(*) Information on Stroke at baseline provided in datasets from countries = ARG; AUS; AUT; BGR; CHE; CHL; CHN; CYP; DEU; ESP; GBR; GRC; HRV; HUN; IND; IRL; IRN; IRQ; ISR; JPN; LBN; MEX; MYS; NLD; POL; PRT; RUS; SAU; SGP; SVK; SVN; THA; TWN; UKR; URY; UZB; VEN; VNM; ZAF
Lipid-lowering medication	10,428 (92·9%)	618 (100%)	11046 (93·2%)	
Total cholesterol	8,774 (78·1%; excluding NLD: 63.4%) *	566 (91·6%)	Presented separately	(*) NLD: available data 3210 (36.6%). In NLD all cases are genetically confirmed FH
LDL-cholesterol	8,566 (76·3%; excluding NLD: 64.6%) *	599 (96·9%)	Presented separately	(*) NLD: available data 3031 (35.4%). In NLD all cases are genetically confirmed FH
HDL-cholesterol	8,636 (76·9%; excluding NLD: 63.0%) *	572 (92·6%)	Presented separately	(*) NLD: available data 3193 (37.0%). In NLD all cases are genetically confirmed FH
Triglycerides	7,080 (63·0%; excluding NLD: 55.5%) *	555 (89·8%)	Presented separately	(*) NLD: available data 3151 (44.5%). In NLD all cases are genetically confirmed FH

Data shown as absolute and relative frequencies [n (%)]. France registry (French Registry of Familial HypERCHOLesterolaemia, REFERCHOL): unable to share individual-level data due to regulatory restrictions. FH, familial hypercholesterolaemia; FHSC, Familial Hypercholesterolaemia Studies Collaboration; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Country codes: ARG, Argentina; AUS, Australia; AUT, Austria; BEL, Belgium; BGR, Bulgaria; CAN, Canada; CHE, Switzerland; CHL, Chile; CHN, China; CYP, Cyprus; CZE, Czech Republic; DEU, Germany; ESP, Spain; FRA, France; GBR, United Kingdom; GRC, Greece; HRV, Croatia; HUN, Hungary; IND, India; IRN, Iran; IRQ, Iraq; IRL, Ireland;ISR, Israel; ITA, Italy; JPN, Japan; LBN, Lebanon; MEX, Mexico; MYS, Malaysia; NLD, The Netherlands; NOR, Norway; OMN, Oman; PAK, Pakistan; POL, Poland; PRT, Portugal; RUS, Russia; SAU, Saudi Arabia; SGP, Singapore; SRB, Serbia; SVK, Slovakia; SVN, Slovenia; THA, Thailand; TWN, Taiwan; UKR, Ukraine; URY, Uruguay; UZB, Uzbekistan; VNM, Vietnam; ZAF, South Africa

Supplemental Table 5: Characteristics of children/adolescents with FH by different age categories

		0 to <12 years	12 to <18 years	0 to <9 years	9 to <14 years	14 to <18 years
Total number		7332	3893	5040	3707	2478
Sex	Boys	3570 (50·2)	1855 (49·6)	2429 (49·7)	1839 (51·0)	1157 (48·9)
	Girls	3543 (49·8)	1885 (50·4)	2456 (50·3)	1764 (49·0)	1208 (51·1)
Age at registry entry (years)		7·0 (4·0-9·4)	14·7 (13·0-16·1)	5·3 (3·0-7·0)	11·1 (10·0-12·5)	15·9 (14·9-17·0)
Age at FH diagnosis (years)		7·0 (4·0-9·3)	14·3 (12·9-16·0)	5·0 (3·0-7·1)	11·0 (9·8-12·3)	15·6 (14·6-16·8)
Index Cases		2549 (38·0)	776 (22·3)	2001 (42·9)	870 (26·3)	454 (20·5)
Corneal Arcus		21 (0·7)	18 (1·3)	10 (0·4)	12 (0·8)	17 (2·0)
Xanthoma		59 (1·6)	54 (3·9)	31 (1·1)	43 (2·8)	39 (4·7)
Hypertension		11 (0·2)	14 (0·5)	6 (0·2)	8 (0·3)	11 (0·6)
Diabetes Mellitus		17 (0·4)	10 (0·3)	11 (0·4)	8 (0·3)	8 (0·4)
Smoking		15 (0·3)	243 (8·0)	3 (0·1)	29 (1·0)	226 (11·5)
0-<5 years		16·7 (15·2-18·1)	--	16·7 (15·2-18·1)	--	--
5-<10 years		16·0 (14·8-17·6)	--	15·7 (14·6-17·3)	16·8 (15·3-19·2)	--
10-<15 years		17·6 (15·9-20·3)	19·2 (17·4-21·6)	--	18·2 (16·4-20·8)	19·9 (18·1-22·2)
15-<18 years		--	21·1 (19·5-23·5)	--	--	21·1 (19·5-23·5)
Coronary Artery Disease		10 (0·2)	15 (0·4)	7 (0·2)	7 (0·2)	11 (0·5)
Stroke		2 (0·04)	0	1 (0·03)	1 (0·04)	0
Lipid-Lowering Medication (LLM)		1710 (25·5)	1161 (31·9)	1063 (23·2)	1051 (30·0)	757 (33·1)
Participants Not on LLM		6·96 (5·90-7·97)	6·40 (5·45-7·53)	7·06 (6·03-8·02)	6·52 (5·60-7·61)	6·39 (5·40-7·60)
Participants On LLM		6·11 (5·22-7·24)	5·81 (4·87-6·91)	6·07 (2·25-7·09)	6·08 (5·12-7·30)	5·75 (4·85-6·90)
Participants Not on LLM		5·12 (4·19-6·21)	4·70 (3·79-5·76)	5·25 (4·30-6·30)	4·73 (3·84-5·79)	4·75 (3·80-5·87)
Participants On LLM		4·46 (3·63-5·48)	4·15 (3·26-5·20)	4·40 (3·68-5·40)	4·40 (3·46-544)	4·13 (3·19-5·13)
Participants Not on LLM		1·34 (1·13-1·58)	1·23 (1·01-1·47)	1·34 (1·13-1·58)	1·32 (1·11-1·55)	1·20 (0·99-1·42)
Participants On LLM		1·20 (1·00-1·42)	1·17 (1·00-1·40)	1·15 (0·95-1·38)	1·24 (1·06-1·45)	1·14 (0·96-1·37)
Participants Not on LLM		0·84 (0·62-1·19)	0·94 (0·69-1·40)	0·80 (0·61-1·16)	0·90 (0·67-1·30)	0·99 (0·70-1·45)
Participants On LLM		0·85 (0·60-1·22)	0·89 (0·64-1·23)	0·86 (0·61-1·26)	0·85 (0·61-1·19)	0·89 (0·64-1·29)

Data are presented as median (IQR) for continuous variables or n (%) for categorical variables. FH=familial hypercholesterolaemia. NA=not applicable

Supplemental Table 6: Characteristics of children and adolescents with FH stratified by World Health Organisation (WHO) regions

		WHO Regions					
		African*	Americas	Eastern Mediterranean	European (excluding the Netherlands)	The Netherlands	South-East Asia & Western Pacific
Total number		139	431	118	5524	5473	163
Sex	Boys	69 (49·6%)	177 (43·5%)	63 (53·4%)	2520 (48·7%)	2799 (51·1%)	92 (56·4%)
	Girls	70 (50·4%)	230 (56·5%)	55 (46·6%)	2656 (51·3%)	2674 (48·9%)	71 (43·6%)
Age at registry entry (years)		12·0 (9·0-14·5)	12·0 (8·0-15·0)	12·4 (7·0-15·1)	8·0 (4·0-12·0)	10·5 (7·0-14·2)	11·5 (8·0-14·7)
Age at FH diagnosis (years)		12·0 (9·0-14·0)	11·3 (8·0-15·0)	12·7 (7·0-15·1)	7·0 (3·0-11·0)	10·5 (7·0-14·2)	11·4 (7·6-14·5)
Index cases		§	25 (22·7%)	16 (17·0%)	3435 (79.5)	360 (6·6%)	18 (11·4%)
Corneal arcus		2 (5·7%)	7 (2·1%)	3 (4·0%)	28 (0·6%)	§	3 (1·9%)
Xanthoma		8 (5·8%)	30 (7·3%)	8 (9·9%)	72 (1·5%)	§	7 (10·6%)
Hypertension		0	7 (1·8%)	2 (4·1%)	15 (0·7%)	3 (0·1%)	§
Diabetes mellitus		§	2 (0·5%)	5 (9·8%)	15 (0·8%)	9 (0·2%)	1 (0·7%)
Smoking		8 (6·2%)	40 (11·8%)	§	38 (1·3%)	185 (3·4%)	§
Body Mass Index (kg/m²)							
0-<5 years		§	15·5 (14·7-16·6)	22·3 (19·5-26·9)	17·2 (15·9-18·4)	15·3 (14·2-16·8)	13·1 (12·4-14·9)
5-<10 years		§	16·4 (15·0-18·4)	17·7 (17·4-18·0)	16·2 (14·9-18·2)	15·8 (14·6-17·3)	16·7 (13·5-18·4)
10-<15 years		§	19·3 (17·4-22·7)	24·2 (21·5-31·0)	19·7 (17·1-22·6)	18·0 (16·4-20·1)	16·9 (15·1-18·8)
15-<18 years		§	22·5 (20·6-25·8)	27·1 (23·0-27·7)	21·9 (20·0-24·9)	20·7 (19·3-22·7)	18·9 (18·1-22·6)
Coronary artery disease		9 (6·5%)	§	3 (4·9%)	13 (0·3%)	2 (0·04%)	0
Stroke		§	§	§	2 (0·1%)	0	§
Lipid-Lowering Medication (LLM)		104 (75·9%)	87 (25·7%)	44 (41·9%)	946 (19·6%)	1936 (35·4%)	26 (16·5%)
Total cholesterol, mmol/L							
Participants Not on LLM		7·70 (6·60-9·30)	7·41 (6·60-8·30)	7·20 (5·50-8·20)	7·19 (6·23-8·17)	7·20 (6·26-8·20)	7·15 (6·10-8·40)
Participants On LLM		5·85 (5·00-6·70)	8·10 (7·00-9·31)	6·80 (5·17-8·60)	6·39 (5·30-7·50)	6·50 (5·30-7·68)	7·01 (4·55-8·30)
LDL-cholesterol, mmol/L							
Participants Not on LLM		6·10 (5·50-7·50)	5·70 (4·90-6·60)	5·20 (3·39-6·00)	5·30 (4·40-6·36)	5·38 (4·42-6·39)	5·49 (4·40-6·60)
Participants On LLM		4·20 (3·30-5·00)	6·10 (5·00-7·24)	4·55 (3·30-5·41)	4·53 (3·56-5·62)	4··62 (3·59-5·72)	5·22 (3·26-6·60)
HDL-cholesterol, mmol/L							
Participants Not on LLM		1·10 (0·90-1·20)	1·10 (1·00-1·30)	1·30 (1·20-1·60)	1·40 (1·22-1·63)	1·40 (1·20-1·60)	1·40 (1·20-1·51)
Participants On LLM		1·20 (0·97-1·40)	1·10 (0·90-1·27)	1·27 (1·10-1·78)	1·40 (1·20-1·60)	1·32 (1·10-1·58)	1·21 (1·10-1·45)
Triglycerides, mmol/L							
Participants Not on LLM		0·92 (0·60-1·15)	1·00 (0·70-1·40)	1·10 (0·75-1·60)	0·80 (0·61-1·08)	0·80 (0·62-1·12)	0·90 (0·63-1·40)
Participants On LLM		1·00 (0·70-1·48)	1·00 (0·75-1·50)	0·84 (0·60-1·35)	0·80 (0·62-1·07)	0·84 (0·64-1·13)	0·82 (0·60-1·00)

Data are presented as median (IQR) for continuous variables or n (%) for categorical variables. *For Africa region, all cases are from South Africa. § Data not available in most cases for these variables from the corresponding region(s). Data available for the variables included in the study are shown in the appendix (pp 20–21). FH=familial hypercholesterolaemia; LLM=lipid-lowering medication; NA=not applicable.

Supplemental Table 7: Characteristics of children/adolescents with FH, stratified by presence of coronary artery disease at entry into the registry

		Presence of Coronary Artery Disease at entry into registry	
		Yes	No
Total Number		25	9842
Age at Registry Entry (years)		12·6 (8·1-17·0)	10·0 (7·0-13·8)
Age at FH diagnosis (years)		12·9 (5·4-17·0)	10·0 (6·7-13·4)
Sex	Boys	15 (62·5)	4733 (99·7)
	Girls	9 (37·5)	4764 (50·2)
Index Case		5 (38·5)	2162 (24·4)
Corneal Arcus		1 (6·7)	36 (1·0)
Xanthoma		2 (14·3)	106 (2·7)
Hypertension		5 (21·7)	18 (0·2)
Diabetes Mellitus		1 (6·7)	22 (0·3)
Smoking		4 (30·8)	254 (3·4)
Total cholesterol, mmol/L			
Participants Not on LLM		7·06 (6·24-7·96)	6·44 (5·50-7·52)
Participants On LLM		6·96 (5·40-8·30)	5·99 (5·08-7·06)
LDL-cholesterol, mmol/L			
Participants Not on LLM		5·51 (4·55-6·57)	4·70 (3·82-5·77)
Participants On LLM		5·27 (4·00-6·50)	4·34 (3·44-5·33)
HDL-cholesterol, mmol/L			
Participants Not on LLM		0·9 (0·85-1·11)	1·28 (1·06-1·5)
Participants On LLM		1·13 (0·95-1·55)	1·19 (1·00-1·40)
Triglycerides, mmol/L			
Participants Not on LLM		1·02 (0·65-1·20)	0·90 (0·66-1·30)
Participants On LLM		1·10 (0·89-1·50)	0·87 (0·62-1·23)

Data are presented as median (IQR) for continuous variables or n (%) for categorical variables. FH=familial hypercholesterolaemia. NA=not applicable. The two cases from France were not included in the above analysis due to unavailability of having the provided data stratified by those with and without CAD.

Supplemental Table 8: Characteristics of children/adolescents with FH, stratified by presence of corneal arcus and xanthomas

		Presence of Corneal Arcus		Presence of Xanthoma	
		Yes	No	Yes	No
Total Number		39	4527	113	4989
Age at registry entry (years)		11·7 (8·0-16·0)	9·0 (4·0-12·4)	11·0 (8·0-15·0)	8·0 (4·0-12·0)
Age at FH diagnosis (years)		10·0 (7·0-15·2)	7·0 (3·0-11·2)	11·0 (8·8-15·0)	7·5 (4·0-11·0)
Sex	Boys	23 (60·5)	2046 (48·9)	48 (46·2)	2270 (48·8)
	Girls	15 (39·5)	2137 (51·1)	55 (53·4)	2381 (51·2)
Index Case		14 (43·8)	2306 (64·1)	39 (40·6)	2739 (67·9)
Genetic Diagnosis		26 (72·2)	3235 (80·0)	74 (70·5)	3560 (80·3)
Hypertension		3 (15·0)	13 (1·0)	0	20 (1·2)
Diabetes Mellitus		2 (10·0)	11 (0·9)	1 (1·6)	13 (0·8)
Coronary Artery Disease		1 (2·7)	14 (0·4)	2 (1·9)	12 (0·3)
Stroke		0	1 (0·1)	0	1 (0·1)
Total cholesterol, mmol/L					
Participants Not on LLM		8·55 (6·85-9·96)	7·30 (6·39-8·30)	8·52 (7·40-9·80)	7·19 (6·30-8·17)
Participants On LLM		6·45 (6·00-7·19)	6·70 (5·50-7·85)	7·23 (5·59-9·93)	6·69 (5·50-7·80)
LDL-cholesterol, mmol/L					
Participants Not on LLM		6·54 (5·07-8·10)	5·46 (4·50-6·44)	6·74 (5·41-7·69)	5·35 (4·42-6·36)
Participants On LLM		4·54 (4·05-5·20)	4·81 (3·75-6·00)	5·17 (3·52-6·90)	4·80 (3·75-5·92)
HDL-cholesterol, mmol/L					
Participants Not on LLM		1·36 (1·18-1·60)	1·40 (1·20-1·61)	1·31 (1·11-1·70)	1·40 (1·20-1·60)
Participants On LLM		1·24 (1·10-1·32)	1·34 (1·13-1·60)	1·21 (1·09-1·37)	1·34 (1·13-1·60)
Triglycerides, mmol/L					
Participants Not on LLM		1·10 (0·87-1·66)	0·80 (0·62-1·10)	0·80 (0·60-1·30)	0·80 (0·61-1·11)
Participants On LLM		0·70 (0·50-1·15)	0·80 (0·63-1·10)	0·91 (0·60-1·02)	0·80 (0·64-1·10)

Data are presented as median (IQR) for continuous variables or n (%) for categorical variables. FH=familial hypercholesterolaemia. NA=not applicable

Supplemental Table 9: Odds Ratios of having LDL-C ≥7·8 mmol/L (300 mg/dL) amongst children/adolescents not on lipid-lowering medication (LLM)

		LDL-C ≥7·8 mmol/L	Unadjusted	Adjusted by Age	Adjusted by Sex	Adjusted by age and Sex
Sex	Boys	131 (4·9)	1 (ref.)	1 (ref.)	-	-
	Girls	161 (6·0)	1·25 (0·98-1·58)	1·25 (0·98-1·58)	-	-
Age	Per 1-unit (year) increase		0·92 (0·89-0·94)	-	0·92 (0·89-0·94)	-
Age Category	≤9 Years	194 (6·5)	1 (ref.)	-	1 (ref.)	-
	>9 Years	102 (4·2)	0·62 (0·48-0·79)	-	0·61 (0·48-0·78)	-
Corneal Arcus	No	241 (7·9)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
	Yes	7 (26·9)	4·32 (1·80-10·4)	5·01 (2·07-12·15)	4·38 (1·82-10·52)	5·15 (2·12-12·50)
Xanthoma	No	239 (6·8)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
	Yes	13 (5·2)	4·16 (2·21-7·84)	6·24 (3·22-12·09)	3·74 (1·83-7·63)	5·55 (2·65-11·63)
Country Income Status*	Non-High Income	23 (14·8)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
	High-Income	273 (5·2)	0·31 (0·20-0·50)	0·29 (0·18-0·46)	0·31 (0·19-0·49)	0·28 (0·17-0·44)
Diagnostic criteria in first identification step†	No (clinical criteria)	44 (4·3)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
	Yes (genetic only)	75 (2·0)	0·35 (0·21-0·59)	0·35 (0·21-0·59)	0·35 (0·20-0·59)	0·35 (0·20-0·59)

Data are presented as n (%) and odds ratios with 95% confidence intervals. * Included countries in the dataset are classified by income status according to the World Bank year 2023 (Supplemental Table 2). † Diagnostic criteria in first identification are defined as criteria used to first identify FH in children/adolescents, which can be clinical criteria or genetic testing directly (cascade screening) and is illustrated in supplemental figure 2.

Supplemental Table 10: LDL-C levels at registry entry among children/adolescents not receiving lipid-lowering medication, overall and by sex

AGE AT Registry Entry (Years)	Median (IQR)						Number of children/adolescents
	LDL-C mg/dL			LDL-C mmol/L			
	Overall	Boys	Girls	Overall	Boys	Girls	
0-<1	174·4 (150·4-212·7)	121·4 (116·0-167·2)	209·6 (164·7-228·9)	4·51 (3·89-5·50)	3·14 (3·00-4·32)	5·42 (4·26-5·92)	190
1-<2	178·1 (146·2-220·4)	176·9 (145·6-204·4)	188·9 (146·2-239·8)	4·61 (3·78-5·70)	4·58 (3·77-5·29)	4·89 (3·78-6·20)	157
2-<3	231·0 (195·0-266·8)	218·8 (189·0-261·0)	235·7 (205·0-274·0)	5·97 (5·04-6·90)	5·66 (4·89-6·75)	6·10 (5·30-7·09)	466
3-<4	227·0 (197·0-266·0)	226·0 (197·9-264·0)	228·0 (197·0-266·0)	5·87 (5·09-6·88)	5·84 (5·12-6·83)	5·90 (5·09-6·88)	729
4-<5	219·6 (183·0-255·2)	218·2 (183·5-250·0)	220·0 (185·6-259·0)	5·68 (4·73-6·60)	5·64 (4·75-6·47)	5·69 (4·80-6·70)	660
5-<6	193·3 (158·9-228·2)	189·7 (152·0-228·2)	196·0 (166·9-228·2)	5·00 (4·11-5·90)	4·91 (3·93-5·90)	5·07 (4·31-5·90)	691
6-<7	179·0 (143·5-212·7)	179·8 (146·5-212·0)	178·7 (141·0-213·2)	4·63 (3·71-5·50)	4·65 (3·79-5·48)	4·62 (3·65-5·51)	680
7-<8	179·9 (146·9-218·2)	175·9 (147·7-210·0)	180·0 (147·8-222·5)	4·65 (3·80-5·64)	4·54 (3·82-5·43)	4·66 (3·82-5·75)	731
8-<9	185·6 (149·0-226·0)	189·0 (146·0-222·7)	184·1 (150·0-227·8)	4·80 (3·85-5·84)	4·89 (3·78-5·76)	4·76 (3·88-5·89)	736
9-<10	187·9 (150·0-232·0)	182·7 (152·4-234·0)	191·0 (146·0-232·0)	4·86 (3·88-6·00)	4·73 (3·94-6·05)	4·94 (3·78-6·00)	772
10-<11	186·4 (152·7-227·0)	186·0 (155·8-224·8)	187·5 (147·7-228·0)	4·82 (3·95-5·87)	4·81 (4·03-5·81)	4·85 (3·82-5·90)	777
11-<12	182·0 (148·1-228·0)	177·9 (146·8-225·2)	183·1 (148·7-228·2)	4·71 (3·83-5·90)	4·60 (3·80-5·82)	4·74 (3·85-5·90)	743
12-<13	183·0 (146·9-220·0)	180·7 (145·0-219·6)	186·8 (150·3-220·4)	4·73 (3·80-5·69)	4·67 (3·75-5·68)	4·83 (3·89-5·70)	741
13-<14	176·1 (145·6-212·3)	167·6 (138·8-212·0)	181·4 (150·0-213·0)	4·55 (3·77-5·49)	4·33 (3·59-5·48)	4·69 (3·88-5·51)	674
14-<15	176·7 (141·0-218·0)	169·1 (131·0-218·0)	185·6 (149·7-220·0)	4·57 (3·65-5·64)	4·37 (3·39-5·64)	4·80 (3·87-5·69)	662
15-<16	198·4 (154·1-240·0)	186·9 (152·0-225·6)	203·5 (160·5-243·8)	5·13 (3·99-6·21)	4·83 (3·93-5·83)	5·26 (4·15-6·31)	612
16-<17	173·8 (137·7-221·0)	165·3 (130·3-212·7)	181·0 (146·9-232·0)	4·49 (3·56-5·72)	4·28 (3·37-5·50)	4·68 (3·80-6·00)	580
17-<18	190·5 (152·0-226·6)	170·5 (138·4-210·0)	200·5 (170·0-231·0)	4·93 (3·93-5·86)	4·41 (3·58-5·43)	5·19 (4·40-5·97)	624

Supplemental Table 11: LDL-C levels at the time of FH diagnosis among children/adolescents not receiving lipid-lowering medication, overall and by sex

Age at FH Diagnosis (years)	Median (IQR)						Number of children/adolescents
	LDL-C mg/dL			LDL-C mmol/L			
	Overall	Boys	Girls	Overall	Boys	Girls	
0-<1	204·1 (150·4-238·6)	145·0 (119·1-224·0)	211·1 (174·4-255·4)	5·28 (3·89-6·17)	3·75 (3·08-5·79)	5·46 (4·51-6·61)	202
1-<2	181·7 (149·0-247·5)	181·7 (150·0-247·5)	190·1 (147·6-247·5)	4·69 (3·85-6·40)	4·70 (3·88-6·40)	4·92 (3·82-6·40)	187
2-<3	231·0 (198·0-267·0)	226·0 (196·0-260·6)	234·0 (199·5-275·0)	5·97 (5·12-6·91)	5·84 (5·07-6·74)	6·05 (5·16-7·11)	621
3-<4	224·0 (197·0-261·0)	224·0 (195·0-261·0)	224·5 (198·0-260·5)	5·79 (5·09-6·75)	5·79 (5·04-6·75)	5·81 (5·12-6·74)	783
4-<5	212·0 (165·6-258·3)	209·0 (162·0-251·7)	216·0 (169·0-265·0)	5·48 (4·28-6·68)	5·41 (4·19-6·51)	5·59 (4·37-6·85)	553
5-<6	193·6 (155·8-231·4)	191·0 (150·8-234·7)	197·2 (158·5-230·0)	5·01 (4·03-5·98)	4·94 (3·90-6·07)	5·10 (4·10-5·94)	578
6-<7	181·4 (143·5-214·0)	182·9 (148·2-213·9)	177·9 (141·0-214·0)	4·69 (3·71-5·53)	4·73 (3·83-6·00)	4·60 (3·65-5·53)	670
7-<8	182·0 (148·0-222·5)	176·7 (147·7-215·0)	185·8 (148·0-222·5)	4·71 (3·83-5·75)	4·57 (3·82-5·56)	4·81 (3·83-5·75)	744
8-<9	184·1 (150·0-224·0)	183·0 (149·0-218·0)	184·9 (150·0-224·3)	4·76 (3·88-5·79)	4·73 (3·85-5·64)	4·78 (3·88-5·80)	730
9-<10	186·7 (147·3-227·8)	183·3 (150·4-226·9)	188·0 (145·4-226·2)	4·83 (3·81-5·89)	4·74 (3·89-5·87)	4·86 (3·76-5·85)	753
10-<11	182·5 (153·2-223·0)	184·0 (158·5-224·3)	181·0 (144·0-222·4)	4·72 (3·97-5·78)	4·76 (4·10-5·80)	4·68 (3·72-5·75)	759
11-<12	180·0 (149·3-224·0)	174·0 (141·1-222·0)	181·9 (158·9-224·0)	4·66 (3·86-5·79)	4·50 (3·65-5·74)	4·70 (4·10-5·79)	693
12-<13	181·2 (150·0-219·3)	175·4 (144·2-216·6)	188·4 (152·2-220·7)	4·69 (3·88-5·67)	4·54 (3·73-5·60)	4·87 (3·94-5·71)	658
13-<14	179·4 (146·9-212·6)	171·7 (140·3-212·0)	181·7 (151·0-213·0)	4·63 (3·80-5·50)	4·44 (3·63-5·48)	4·70 (3·91-5·51)	619
14-<15	178·7 (143·1-216·6)	164·0 (131·1-211·5)	185·6 (149·7-221·2)	4·62 (3·70-5·60)	4·24 (3·39-5·47)	4·80 (3·87-5·72)	583
15-<16	186·0 (149·7-232·0)	181·4 (140·4-224·3)	193·3 (154·1-240·1)	4·81 (3·87-6·00)	4·69 (3·63-5·80)	5·00 (3·99-6·21)	542
16-<17	173·3 (139·6-220·4)	166·3 (135·3-212·7)	177·9 (146·8-225·4)	4·48 (3·61-5·70)	4·30 (3·50-5·50)	4·60 (3·80-5·83)	522
17-<18	189·5 (151·6-225·1)	171·1 (138·2-209·4)	200·0 (170·0-237·0)	4·90 (3·92-5·82)	4·43 (3·57-5·42)	5·17 (4·40-6·13)	524

Supplemental Table 12: LDL-C values of Non-FH Individuals by age categories

Age Categories	Non-FH Individuals LDL-C Levels				Number of children/Adolescents
	LDL-C mg/dL		LDL-C mmol/L		
	Median (IQR)	Mean (95% CI)	Median (IQR)	Mean (95% CI)	
0 to <9 years	123·7 (108·3-143·1)	124·4 (122·4-126·4)	3·20 (2·80-3·70)	3·22 (3·17-3·27)	626
9 to <14 years	116·4 (104·4-135·3)	117·0 (112·7-121·2)	3·01 (2·70-3·50)	3·03 (2·91-3·13)	149
14 to <18 years	111·0 (92·8-127·6)	109·8 (104·8-114·9)	2·87 (2·40-3·30)	2·84 (2·71-2·97)	133
Age Tertiles					
0 to 6.03 years	123·7 (108·3-143·1)	124·1 (121·0-127·1)	3.20 (2.80-3.70)	3.21 (3.13-3.29)	307
6.04 to 8.56 years	125·7 (108·3-140·2)	124·8 (122·1-127·4)	3.25 (2.80-3.63)	3.23 (3.16-3.29)	304
8.57 to 17.27 years	116·0 (96·7-133·9)	114·7 (111·6-117·9)	3.00 (2.50-3.46)	2.97 (2.89-3.05)	304

Supplemental Table 13: Correlation of LDL-C and triglycerides by age categories amongst children/adolescents not on LLM at registry entry

Age groups Participants Not On LLM	Spearman correlation co-efficient	R^2
0 to <6 years	-0·0596	0·00355
6 to <11 years	0·0530	0·00281
11 to <15 years	0·1366	0·01866
15 to <18years	0·1485	0·02205

Bivariate correlations between LDL-C and triglyceride levels for each age range were performed using the Spearman test to obtain the correlation coefficients showing the strength and direction of the association between both variables. R^2 coefficients were obtained from the correlation coefficients to estimate the percentage of the variability of LDL-C levels that could be explained by the variability on the triglyceride levels.

Supplemental Table 14: Percentage of children/adolescents on LLM by age categories

				Among patients on LLM			Among patients on LLM	
	On LLM	**NOT taking LLM**		**On Statins**	**NOT taking statins**		**On Ezetimibe**	**NOT taking ezetimibe**
Overall	2871 (27·5%)	7557 (72·5%)		814 (29·1%)	1985 (70·9%)		154 (5·7%)	2570 (94·3%)
0 to <5 years	405 (19·1%)	1717 (80·9%)		40 (10·0%)	360 (90·0%)		17 (4·3%)	377 (95·7%)
5 to <10 years	957 (27·2%)	2559 (72·8%)		230 (24·6%)	705 (75·4%)		46 (5·0%)	867 (95·0%)
10 to <15 years	940 (30·4%)	2148 (69·6%)		317 (34·8%)	593 (65·2%)		49 (5·6%)	830 (94·4%)
15 to <18 years	569 (33·4%)	1133 (66·6%)		227 (41·0%)	327 (59·0%)		42 (7·8%)	496 (92·2%)

The data shows that 40 and 17 cases aged 0-5 years were on statins and on ezetimibe, respectively. While these agents are not licenced for use in children this young, the prescription of statins and ezetimibe in this age group is made, ultimately, at the discretion of the physician. In our study we are simply reporting what is happening in a real-world setting for management of FH in children/adolescents. From the French dataset, 272 children/adolescents were on lipid lowering medication (LLM) but the categorisation of these children/adolescents by different age groups and type of medications were not available.

Supplemental Table 15: Odds ratios of having an LDL-C <3·4 mmol/L (<130 mg/dl) amongst children/adolescents on lipid-lowering medication at registry entry

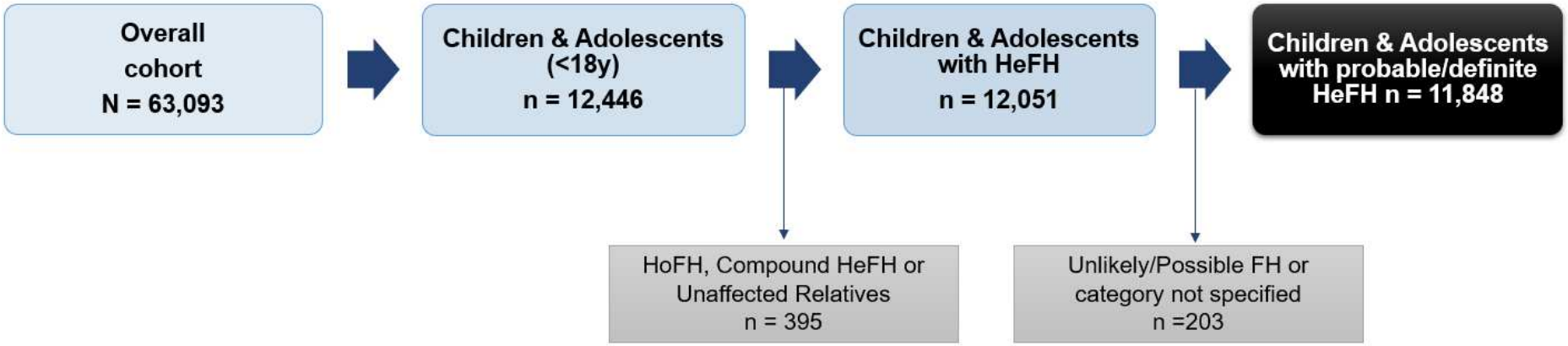
	LDL-C <3·4 mmol/L		Unadjusted	Adjusted by Age	Adjusted by Sex	Adjusted by age and Sex	Adjusted by age, Sex and taking statins	Adjusted by age, Sex and taking both statins + ezetimibe
Sex	Boys	306 (25·6%)	1 (ref.)	1 (ref.)	-	-	1 (ref.)	1 (ref.)
	Girls	250 (20·2%)	0·74 (0·61-0·89)	0·73 (0·62-0·88)	-	-	0·74 (0·61-0·89)	0·74 (0·61-0·90)
Age	Per 1 unit (year) increase		1·06 (1·04-1·09)	-	1·06 (1·04-1·09)	-	1·06 (1·04-1·09)	1·06 (1·03 1·08)
Age Category	≤9 Years	158 (18·1)	1 (ref.)	-	1 (ref.)	-	1 (ref.)	1 (ref.)
	>9 Years	401 (25·6)	1·56 (1·27-1·92)	-	1·54 (1·25-1·90)	-	1·04 (0·73-1·48)	1·07 (0·75-1·52)
Country Income Status*	NHIC	41 (23·0)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
	HIC	518 (22·9)	0·99 (0·69-1·42)	1·01 (0·70-1·45)	0·98 (0·68-1·41)	1·00 (0·69-1·44)	1·04 (0·71-1·52)	1·04 (0·72-1·50)
Taking statins	Not taking statins	369 (22·6%)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	-	-
	Taking statins	186 (25·1%)	1·14 (0·93-1·40)	1·03 (0·84-1·27)	1·13 (0·92-1·38)	1·02 (0·83-1·26)	-	-
Taking statins and/or ezetimibe	Not taking any of both	350 (22·3%)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	-	-
	Taking only 1 of statin or ezetimibe	139 (24·1%)	1·11 (0·88-1·39)	1·01 (0·80-1·26) p	1·09 (0·87-1·36)	0·99 (0·79-1·25)	-	-
	Taking both statin + ezetimibe	36 (36·4%)	1·92 (1·30-3·05)	1·83 (1·19-2·82)	1·99 (1·30-3·06)	1·83 (1·19-2·82)	-	-

Data are presented as n (%) and odds ratios with 95% confidence intervals * Included countries in the dataset are classified by income status according to the World Bank year 2023 (supplemental table 2).

SUPPLEMENTAL FIGURES

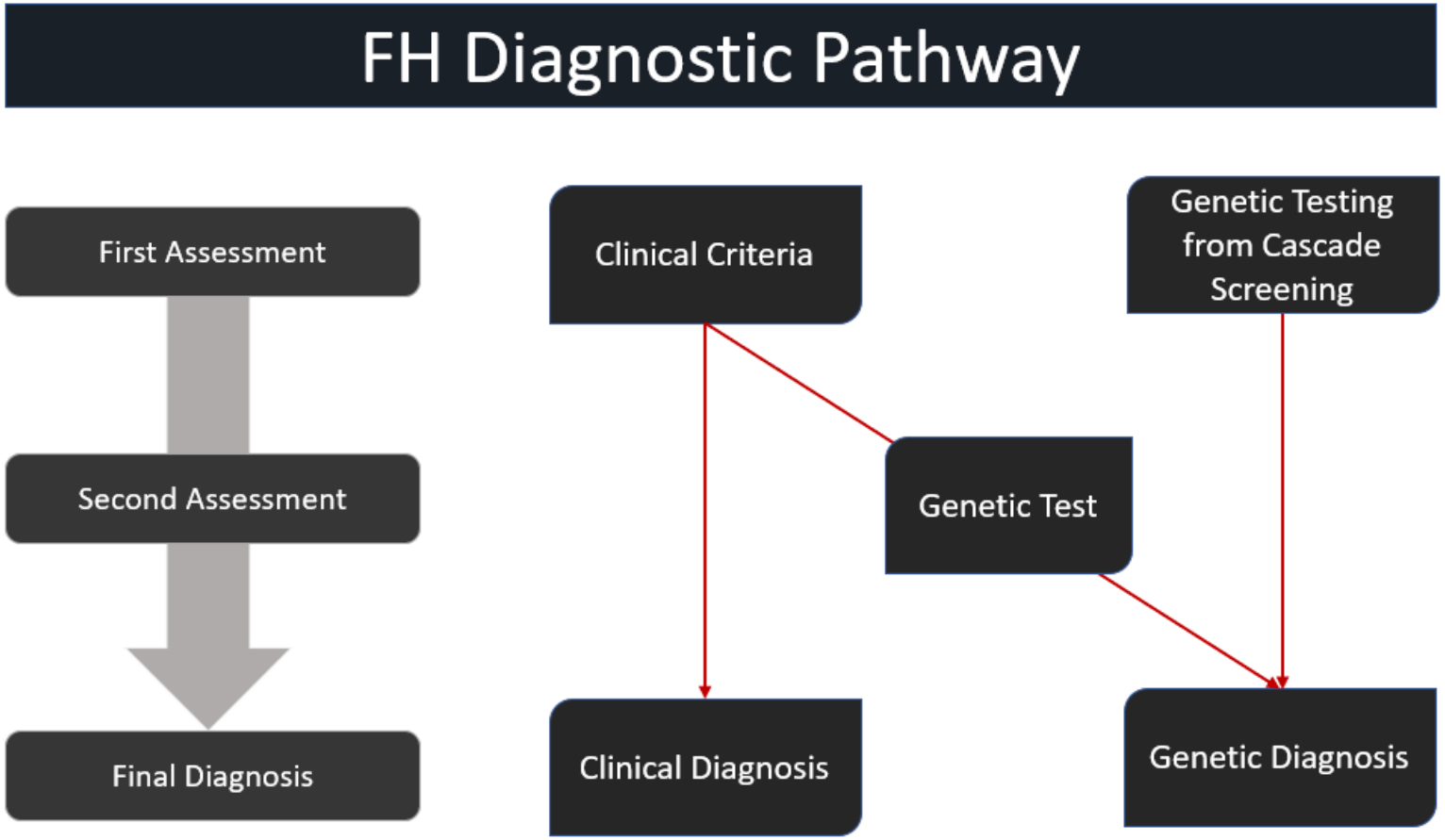
Supplementary Figure 1: Selection of children/adolescents with Heterozygous Familial Hypercholesterolaemia for inclusion in this study from the overall FHSC Registry

Further details are described in the Methods section of the Article. FH, Familial Hypercholesterolaemia; HeFH, Heterozygous Familial Hypercholesterolaemia; HoFH, Homozygous Familial Hypercholesterolaemia; y, years.



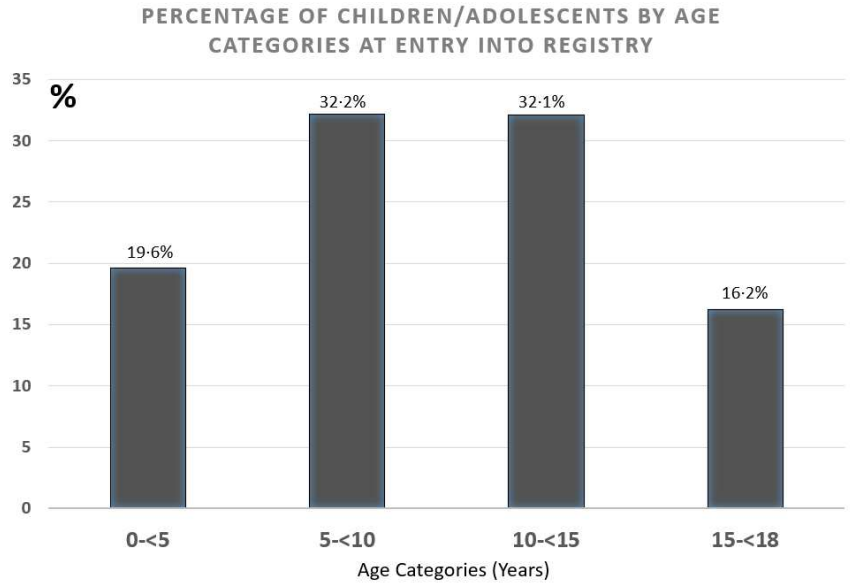
Supplemental Figure 2: Diagnostic process pathway considered for analysis

The initial identification step consists of screening children either through clinical criteria or undergoing genetic testing (due to cascade testing). Children/adolescents suspected of having FH following an initial assessment with the clinical criteria will undergo a genetic test (if available) or this group will be diagnosed solely through the clinical criteria. The final diagnosis is made either through genetics or clinical criteria.

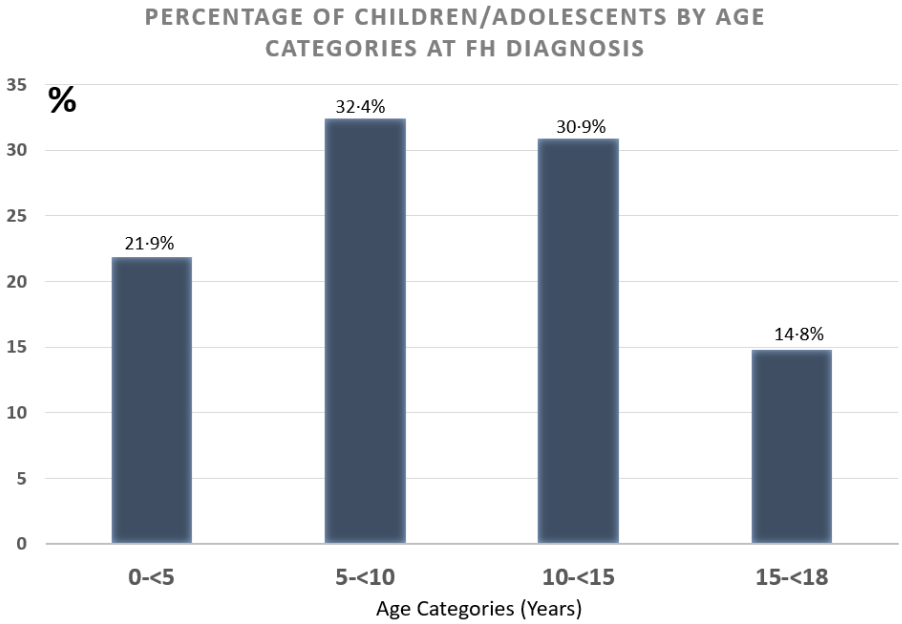


Supplementary Figure 3: Distribution of children and adolescents by age at registry entry and age at diagnosis of FH

Panel 3A: age at registry entry

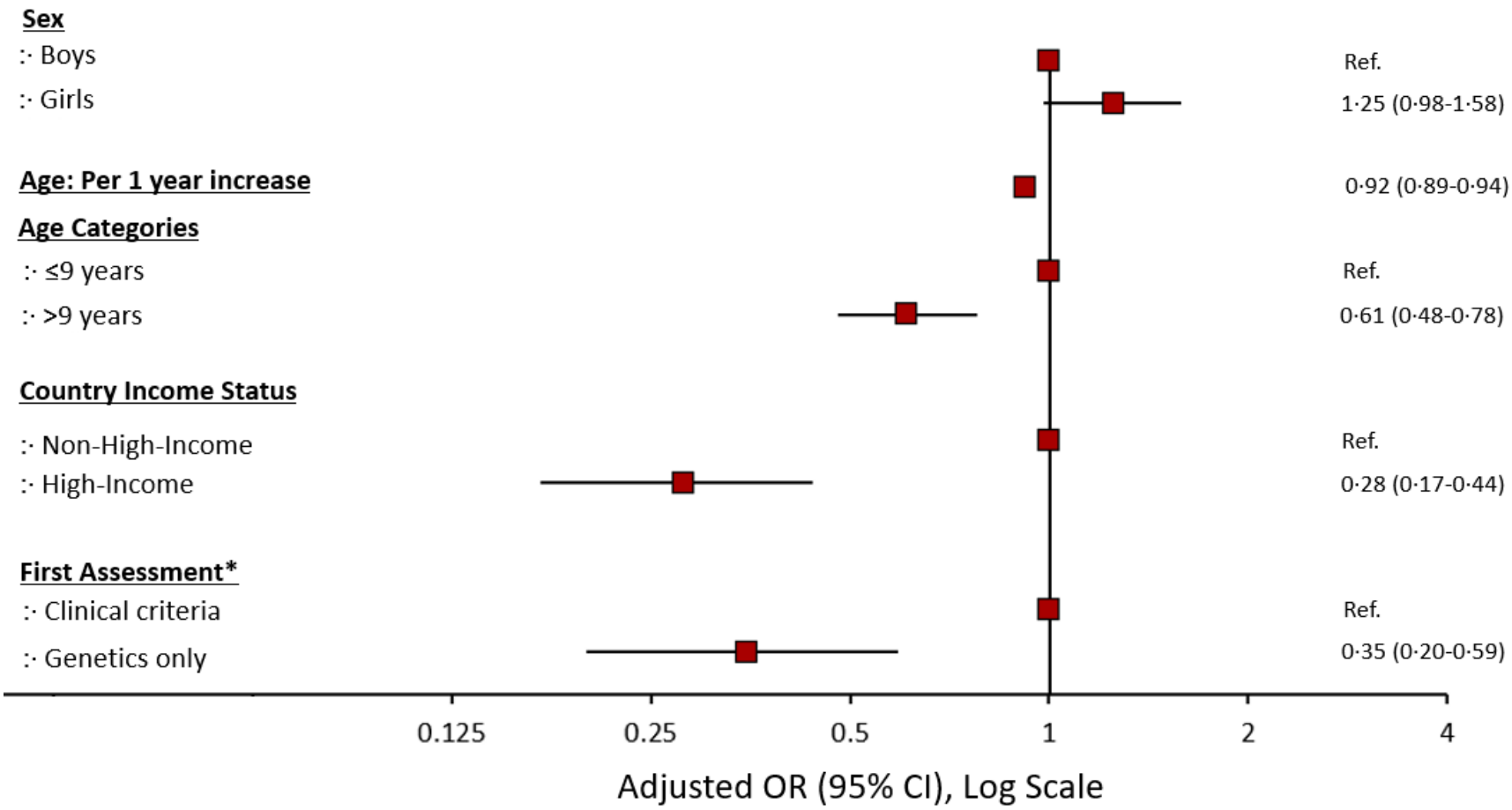


Panel 3B: age at FH diagnosis

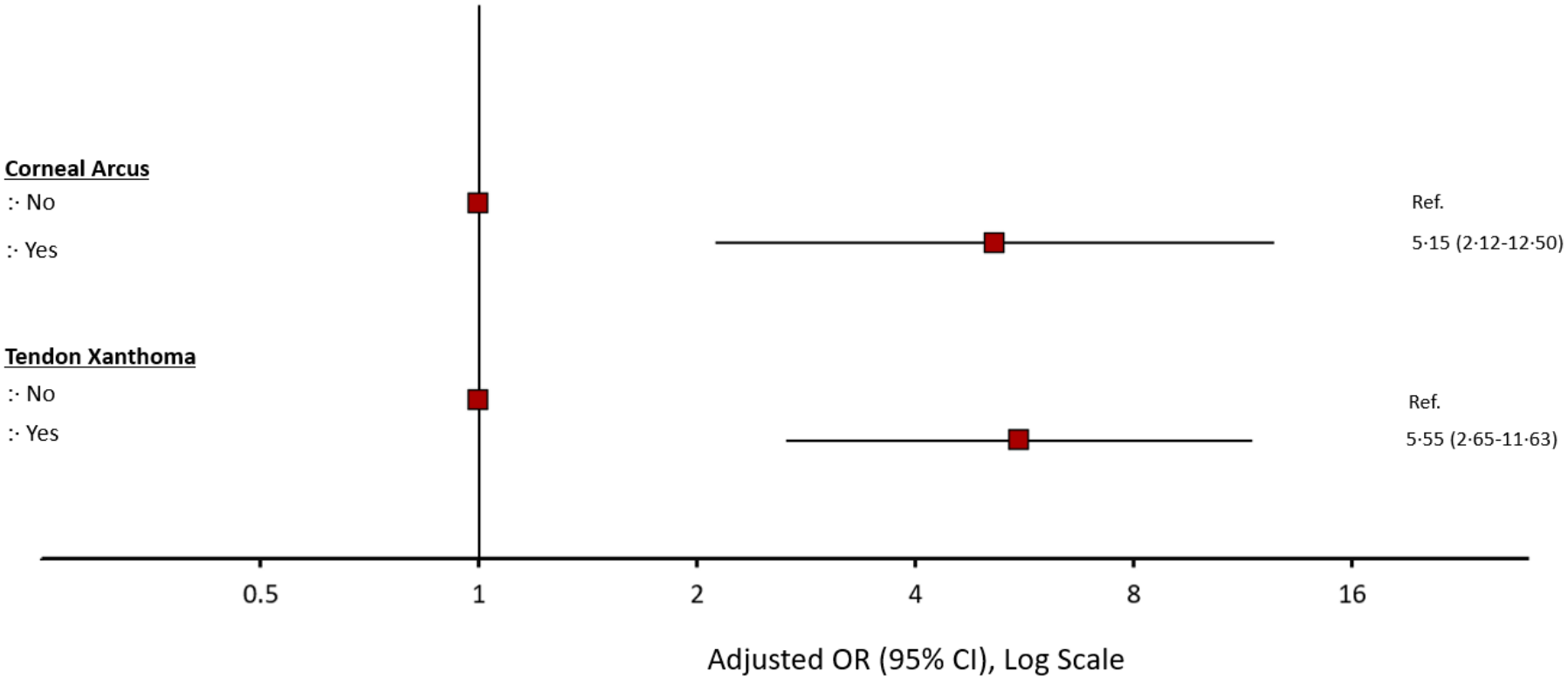


Supplemental Figure 4: Odds ratios for having an LDL-C >7.8 mmol/L amongst children and adolescents not on lipid-lowering medications (LLM)

Panel 4A: Sex is adjusted by age; Age is adjusted by sex; Country income status and first assessment are adjusted by age and sex. *First Assessment refers to diagnostic pathway in figure 1. Supplemental table 9 lists the numbers included in each sub-group alongside the unadjusted and adjusted odds ratios

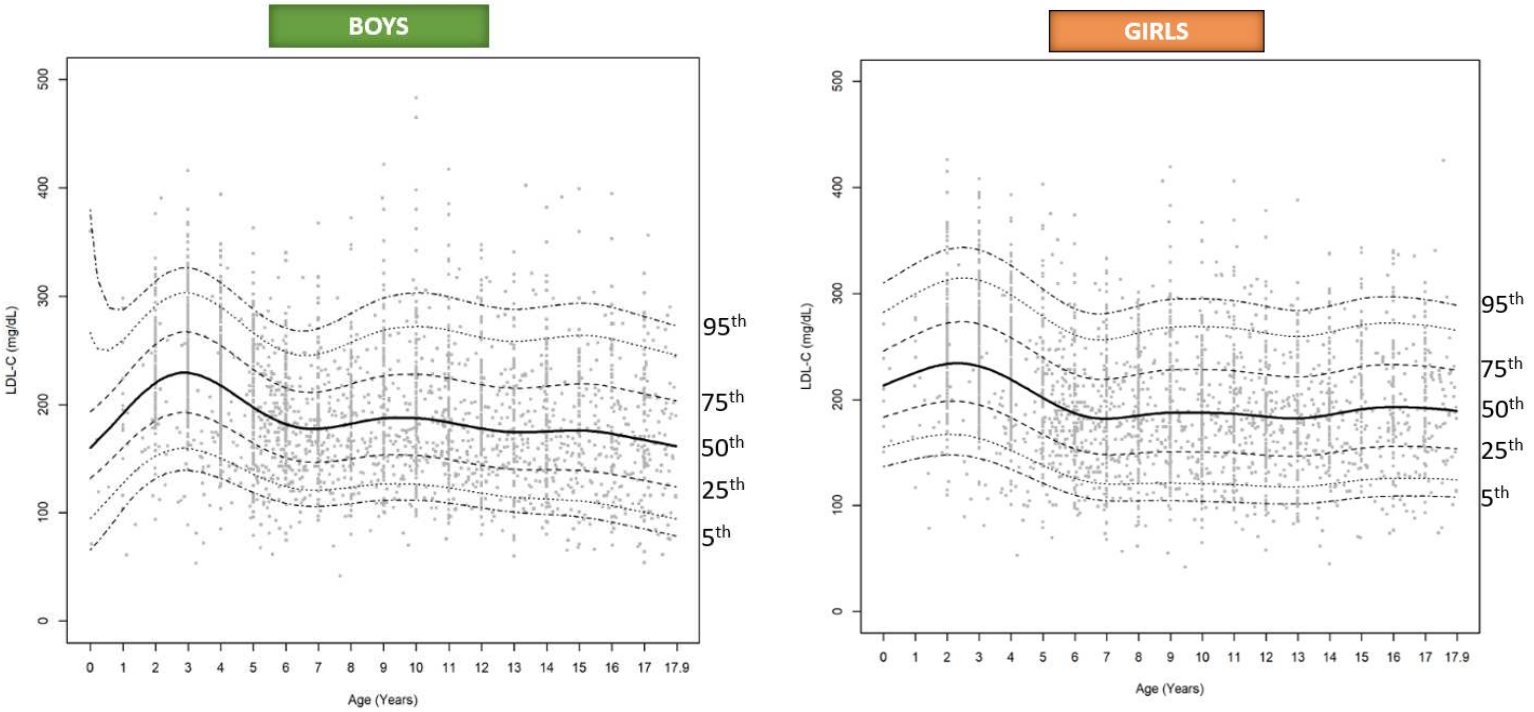


Panel 4B: Physical signs are adjusted by age and sex. Supplemental table 9 lists the numbers included in each sub-group alongside the unadjusted and adjusted odds ratios



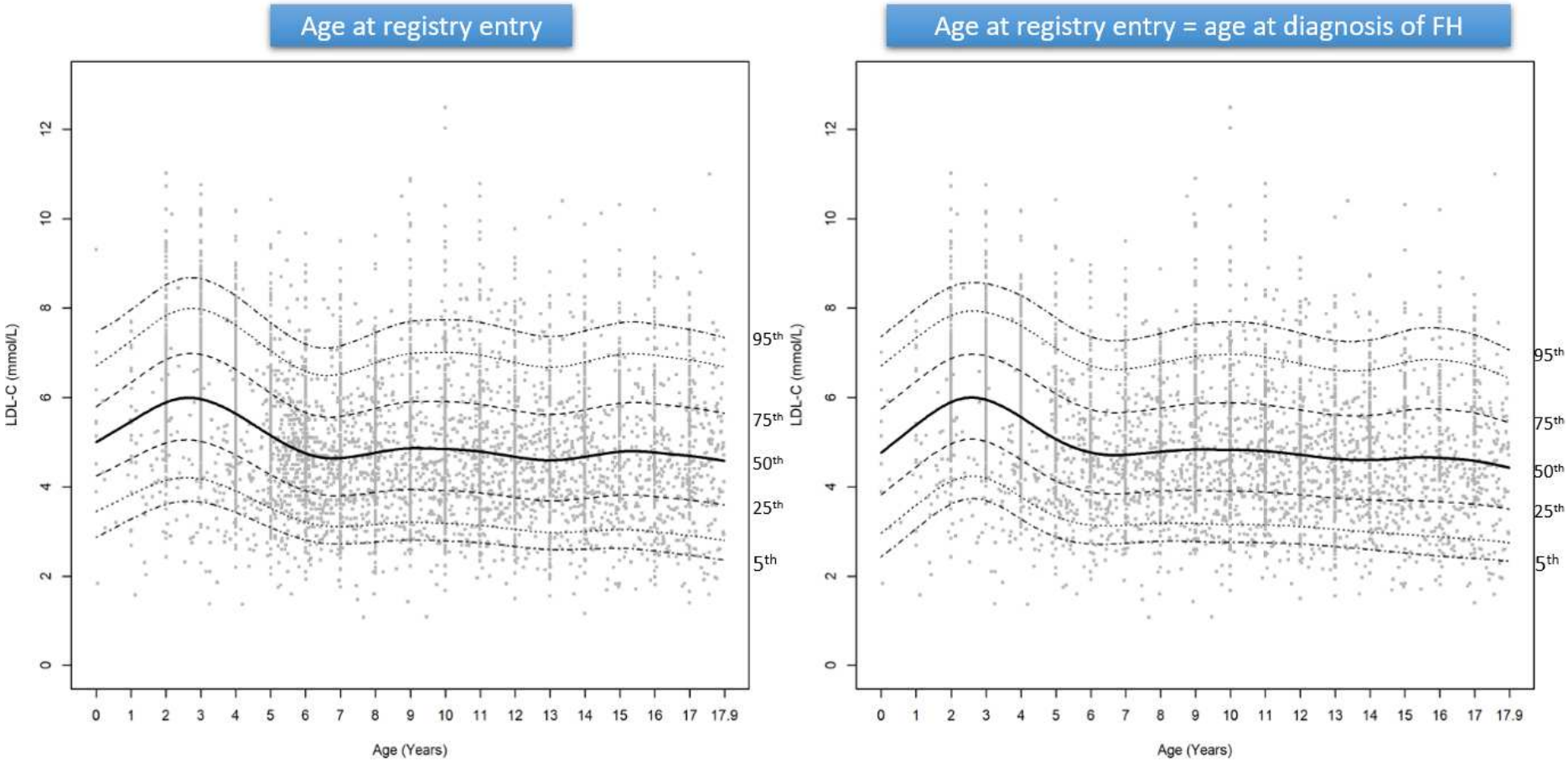
Supplemental Figure 5: Smooth percentile curves for LDL-C (mg/dL) by sex and age for children and adolescents at entry into registry and not on LLM

The two percentiles not labelled are 10th and 90th. Data are cross-sectional, stratified by age.



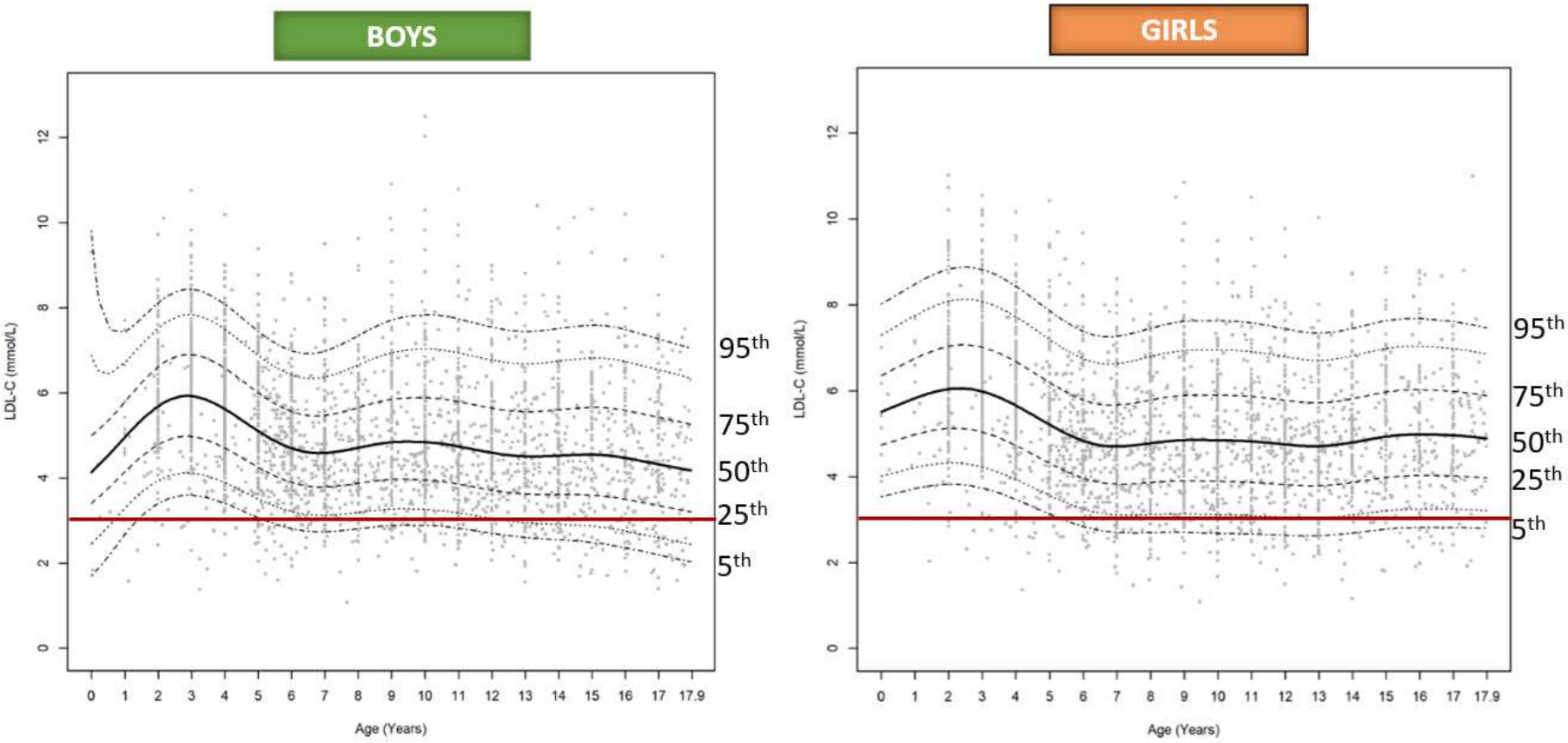
Supplementary Figure 6: Smooth percentile curves for LDL-C (mmol/L) showing age at entry into registry and age at FH diagnosis (where age at diagnosis of FH equals age at entry into registry) amongst children/adolescents not on LLM

The two percentiles not labelled are 10th and 90th. Data are cross-sectional, stratified by age.

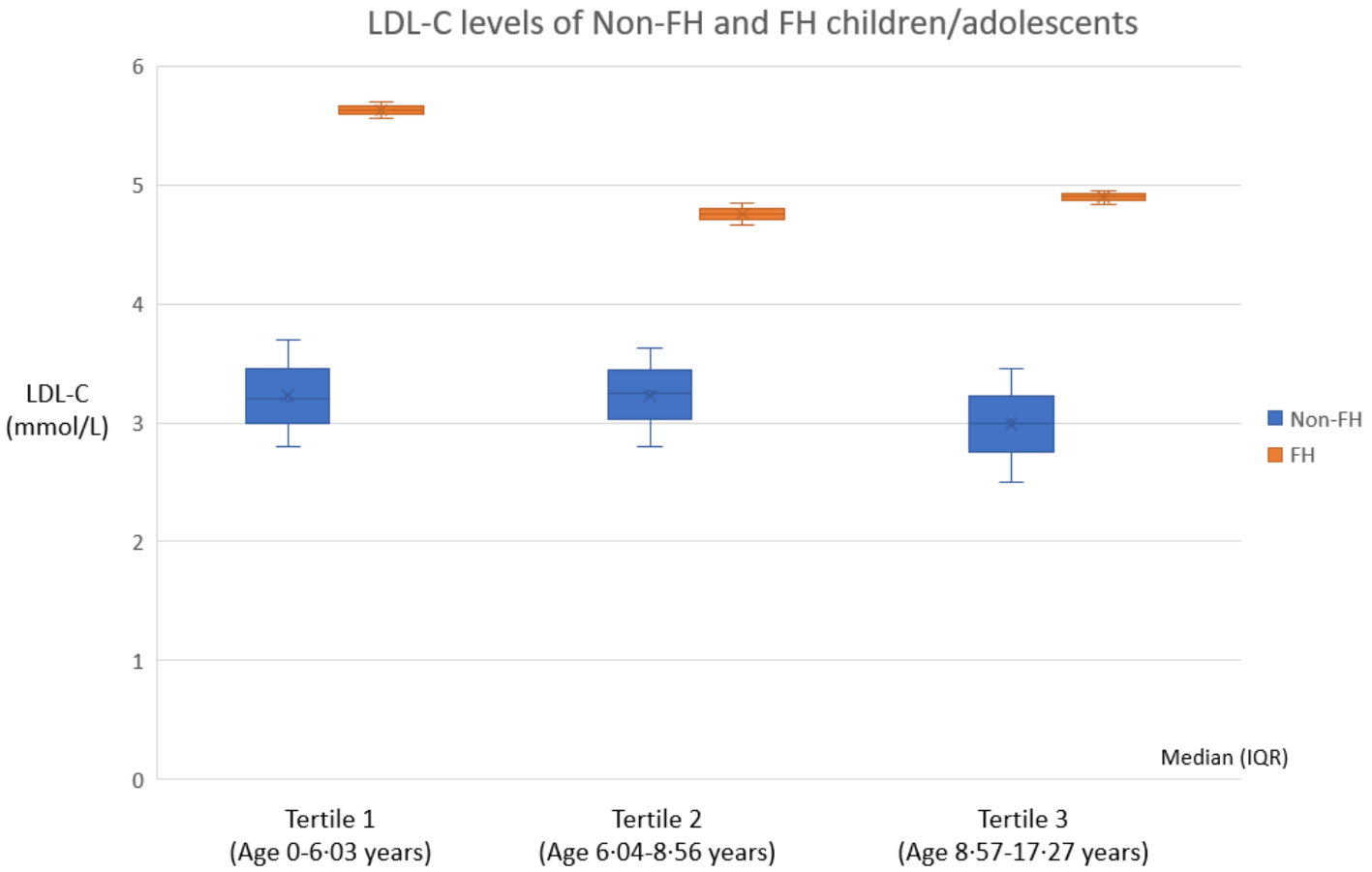


Supplemental Figure 7: Smoothed percentile curves for LDL-C (mmol/L) at entry into registry among children/adolescents not receiving lipid-lowering medication, with median LDL-C of non-FH individuals (horizontal red line)

The two percentiles not labelled are 10th and 90th. Data are cross-sectional, stratified by age

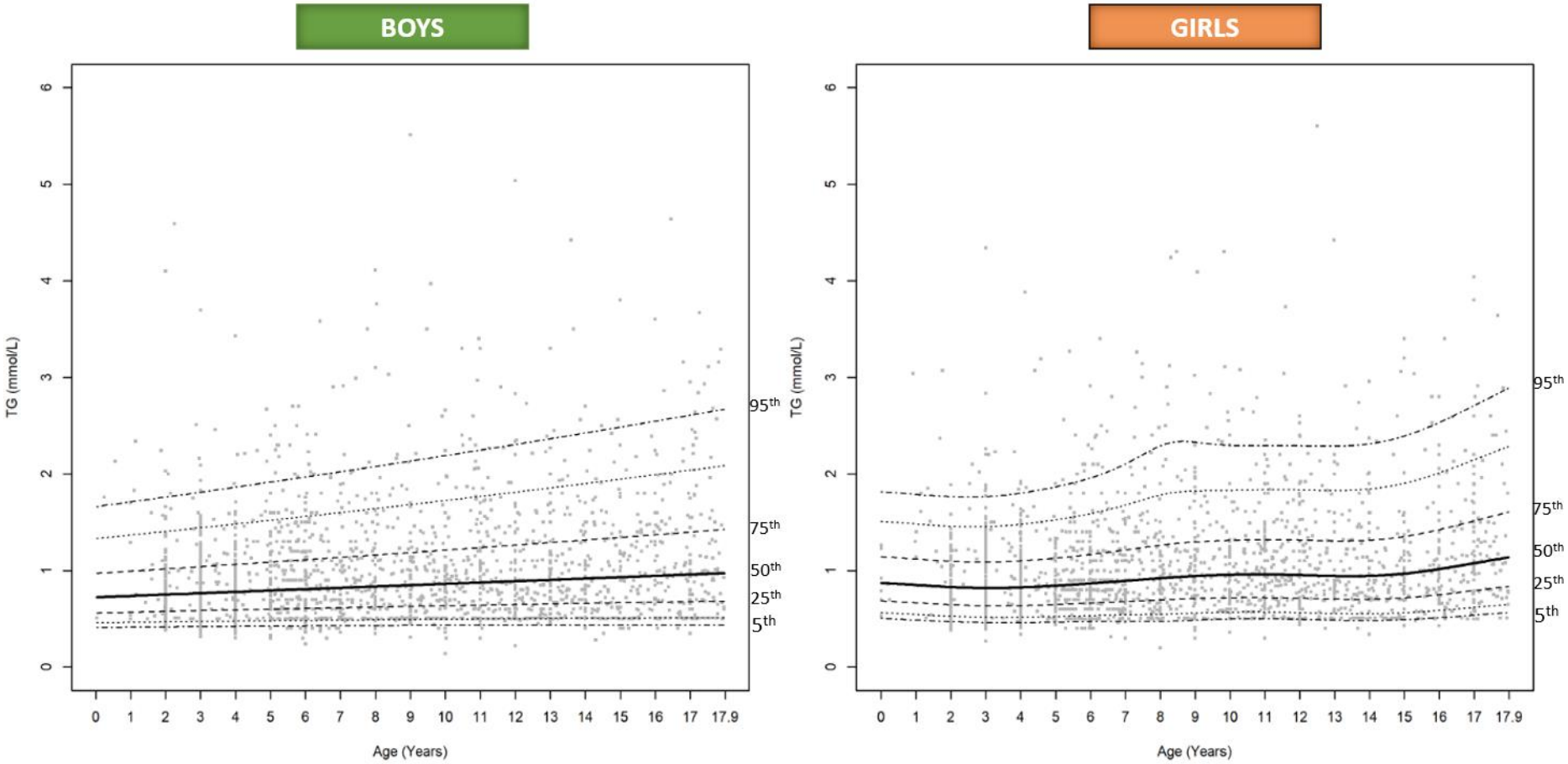


Supplemental Figure 8: Box and whisker plots showing LDL-C levels amongst non-FH and FH children and adolescents by tertiles of age at registry entry



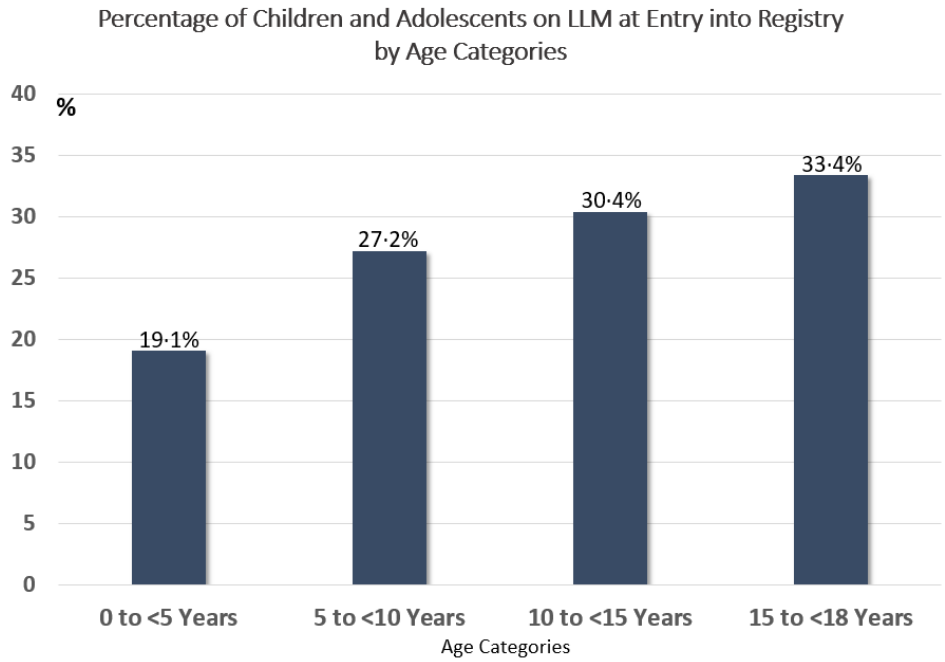
Supplementary Figure 9: Smooth percentile curves for triglyceride (mmol/L) levels at entry into the registry by sex and age amongst children/adolescent not on LLM

The two percentiles not labelled are 10th and 90th. Data are cross-sectional, stratified by age. TG=triglycerides.

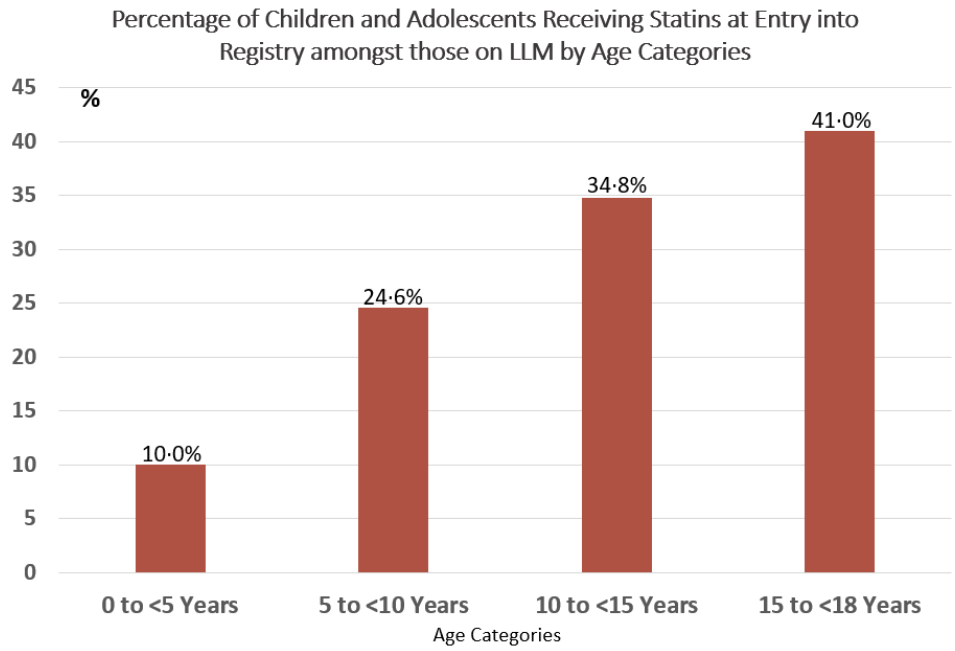


Supplemental Figure 10: Children and adolescents on lipid-lowering medication (LLM) at entry into registries

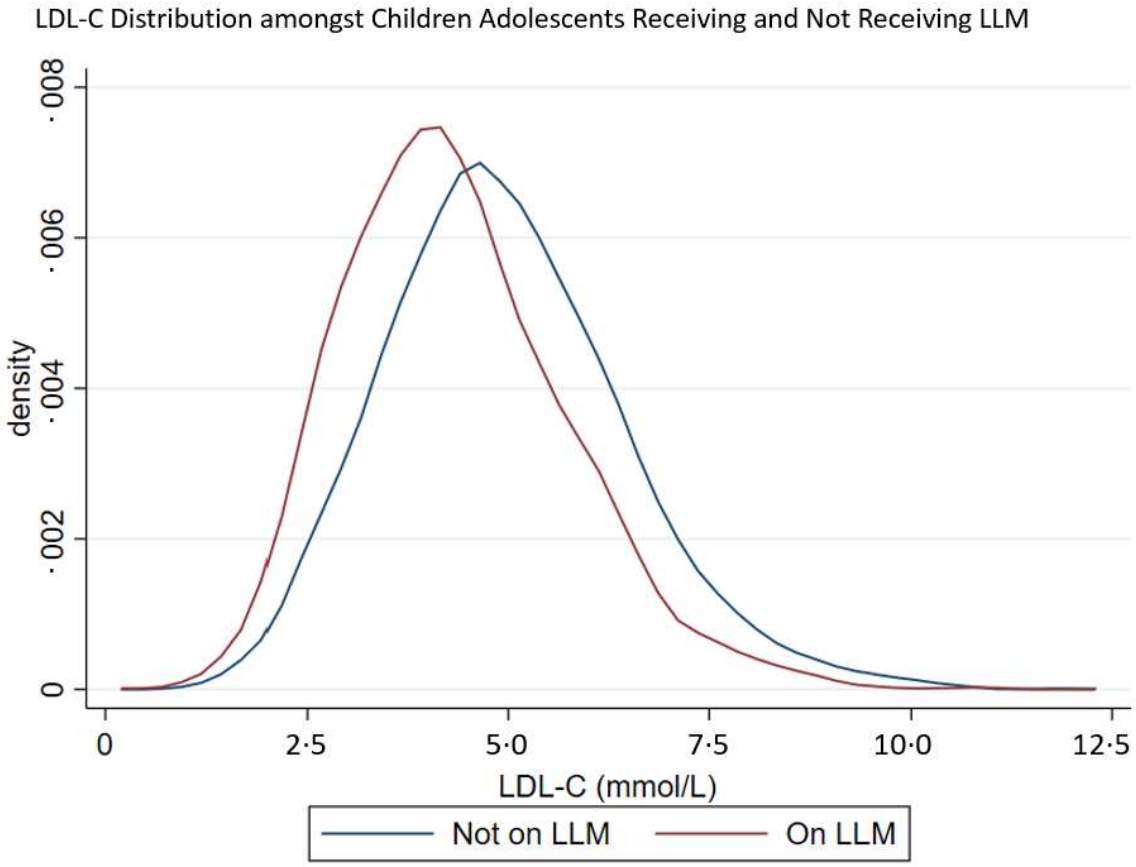
Panel 10A: Percentage of children/adolescents on lipid-lowering medication (LLM) at entry into registry by age categories



Panel 10B: Percentage of children/adolescents receiving Statins amongst those on lipid-lowering medication (LLM) at entry into registry by age categories



Panel 10C: LDL-C distribution amongst children and adolescents receiving and not receiving lipid-lowering medication (LLM) at entry into the registry. Kernel density estimation to produce probability density functions to show smooth distributions of non-parametric LDL-C.



Supplemental References

1. Corral P, Geller AS, Polisecki EY, et al. Unusual genetic variants associated with hypercholesterolemia in Argentina. Atherosclerosis. 2018;277:256-61.

2. Mehta R, Martagon AJ, Ramirez GA, et al. Familial hypercholesterolemia in Mexico: Initial insights from the national registry. Journal of Clinical Lipidology. 2021;15(1):124-33.

3. Alhabib KF, Al-Rasadi K, Almigbal TH, et al. Familial hypercholesterolemia in the Arabian Gulf region: Clinical results of the gulf fh registry. PLoS One. 2021;16:e0251560.

4. Peretti N, Vimont A, Mas E, et al. Factors predicting statin initiation during childhood in familial hypercholesterolemia: Importance of genetic diagnosis. The Journal of Pediatrics. 2022.

5. Boutari C, Rizos CV, Doumas M, et al. Prevalence of Diabetes and Its Association with Atherosclerotic Cardiovascular Disease Risk in Patients with Familial Hypercholesterolemia: An Analysis from the Hellenic Familial Hypercholesterolemia Registry (HELLAS-FH). Pharmaceuticals. 2022;16:44.

6. Anagnostis P, Rizos CV, Skoumas I, et al. Association between lipoprotein (a) concentrations and atherosclerotic cardiovascular disease risk in patients with familial hypercholesterolemia: an analysis from the HELLAS-FH. Endocrine. 2022;76:324-30.

7. Rizos CV, Skoumas I, Rallidis L, et al. LDL cholesterol target achievement in heterozygous familial hypercholesterolemia patients according to 2019 ESC/EAS lipid guidelines: Implications for newer lipid-lowering treatments. International Journal of Cardiology. 2021;345:119-24.

8. Ceska R, Latkovskis G, Ezhov MV, et al. The impact of the international cooperation on familial hypercholesterolemia screening and treatment: results from the ScreenPro FH Project. Current Atherosclerosis Reports. 2019;21:1-2.

9. Averna M, Cefalu AB, Casula M, et al. Familial hypercholesterolemia: the Italian atherosclerosis society network (LIPIGEN). Atherosclerosis Supplements. 2017;29:11-6.

10. Gazzotti M, Casula M, Bertolini S, et al. The Role of Registers in Increasing Knowledge and Improving Management of Children and Adolescents Affected by Familial Hypercholesterolemia: the LIPIGEN Pediatric Group. Frontiers in Genetics. 2022;13.

11. Ramaswami U, Futema M, Bogsrud MP, et al. Comparison of the characteristics at diagnosis and treatment of children with heterozygous familial hypercholesterolaemia (FH) from eight European countries. Atherosclerosis. 2020;292:178-87.

12. Chlebus K, Cybulska B, Dobrowolski P, et al. Effectiveness and safety of PCSK9 inhibitor therapy in patients with familial hypercholesterolemia within a therapeutic program in Poland: Preliminary multicenter data. Cardiol J. 2022;29:62-71.

13. Gałąska R, Kulawiak-Gałąska D, Chmara M, et al. Aortic valve calcium score in hypercholesterolemic patients with and without low-density lipoprotein receptor gene mutation. PLoS One. 2018 ;13:e0209229.

14. Mickiewicz A, Chmara M, Futema M, et al. Efficacy of clinical diagnostic criteria for familial hypercholesterolemia genetic testing in Poland. Atherosclerosis. 2016;249:52-8

15. Ежов МВ, Близнюк СА, Тмоян НА, et al. Регистр пациентов с семейной гиперхолестеринемией и пациентов очень высокого сердечно-сосудистого риска с недостаточной эффективностью проводимой гиполипидемической терапии (РЕНЕССАНС). Российский кардиологический журнал. 2019:7-13.

16. Bliznyuk SA, Rozhkova TA, Ezhov MV, et al. Predictors of cardiovascular outcomes in patients with heterozygous familial hypercholesterolemia according the Russian familial hypercholesterolemia registry. Atherosclerosis. 2020;315:e193-4.

17. Chubykina UV, Ezhov MV, Afanasieva OI, et al. Elevated lipoprotein (a) level influences familial hypercholesterolemia diagnosis. Diseases. 2022;10(1):6.

18. Bliznyuk S, Chubykina U, Rozhkova T, Ezhov M. Non-Achievement Of Ldl-Cholesterol Goals From The Russian Familial Hypercholesterolemia Registry. Atherosclerosis. 2019;287:e220.

19. Vohnout B, Fábryová Ľ, Klabník A, et alK. Treatment pattern of familial hypercholesterolemia in Slovakia: Targets, treatment and obstacles in common practice. Atherosclerosis. 2018;277:323-6.

20. Gašparovič J, Bašistová Z, Wsólová L, et al. Familial defective apolipoprotein B-100 in Slovakia: are differences in prevalence of familial defective apolipoprotein B-100 explained by ethnicity?. Atherosclerosis. 2007;194:e95-107.

21. Vohnout B, Rašlová K, Gašparovič J, et al. Lipid levels and their genetic regulation in patients with familial hypercholesterolemia and familial defective apolipoprotein B-100: the MEDPED Slovakia Project. Atherosclerosis Supplements. 2003;4:3-5.

22. Ganokroj P, Sunthornyothin S, Siwanuwatn R, et al. Clinical characteristics and treatment outcomes in acromegaly, a retrospective single-center case series from Thailand. Pan African Medical Journal. 2021;40.

23. Harada-Shiba M, Ohta T, Ohtake A, et al. Guidance for pediatric familial hypercholesterolemia 2017. Journal of Atherosclerosis and Thrombosis. 2018;25:539-53.

24. Truong TH, Do DL, Kim NT, et al. Genetics, screening, and treatment of familial hypercholesterolemia: Experience gained from the implementation of the Vietnam familial hypercholesterolemia registry. Frontiers in Genetics. 2020;11:914.