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Supplementary appendix

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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

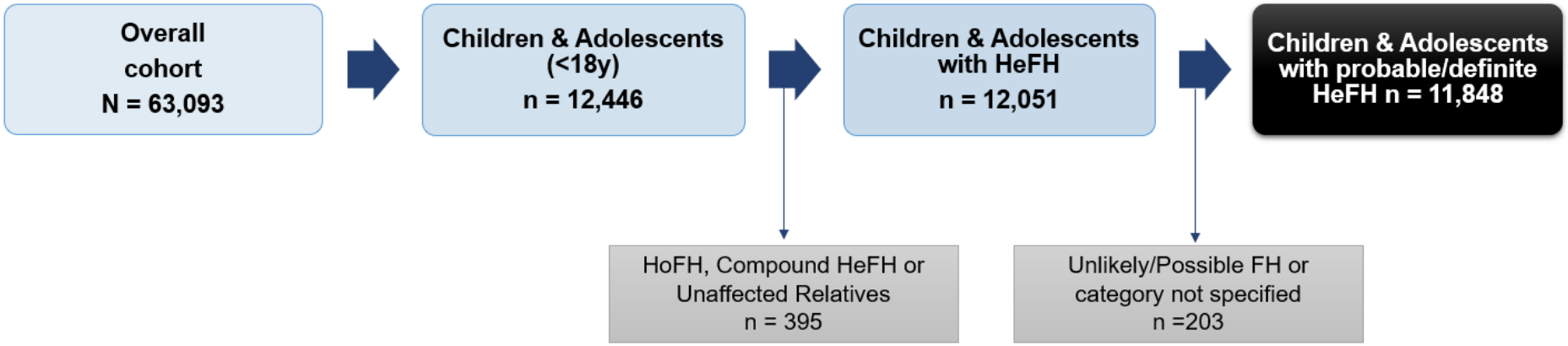
	LDL-C <3·4 mmol/L		Unadjusted	Adjusted by Age	Adjusted by Sex	Adjusted by age and Sex	Adjusted by age, Sex and taking statins	Adjusted by age, Sex and taking both statins + ezetimibe
Sex	Boys	306 (25·6%)	1 (ref.)	1 (ref.)	-	-	1 (ref.)	1 (ref.)
	Girls	250 (20·2%)	0·74 (0·61-0·89)	0·73 (0·62-0·88)	-	-	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

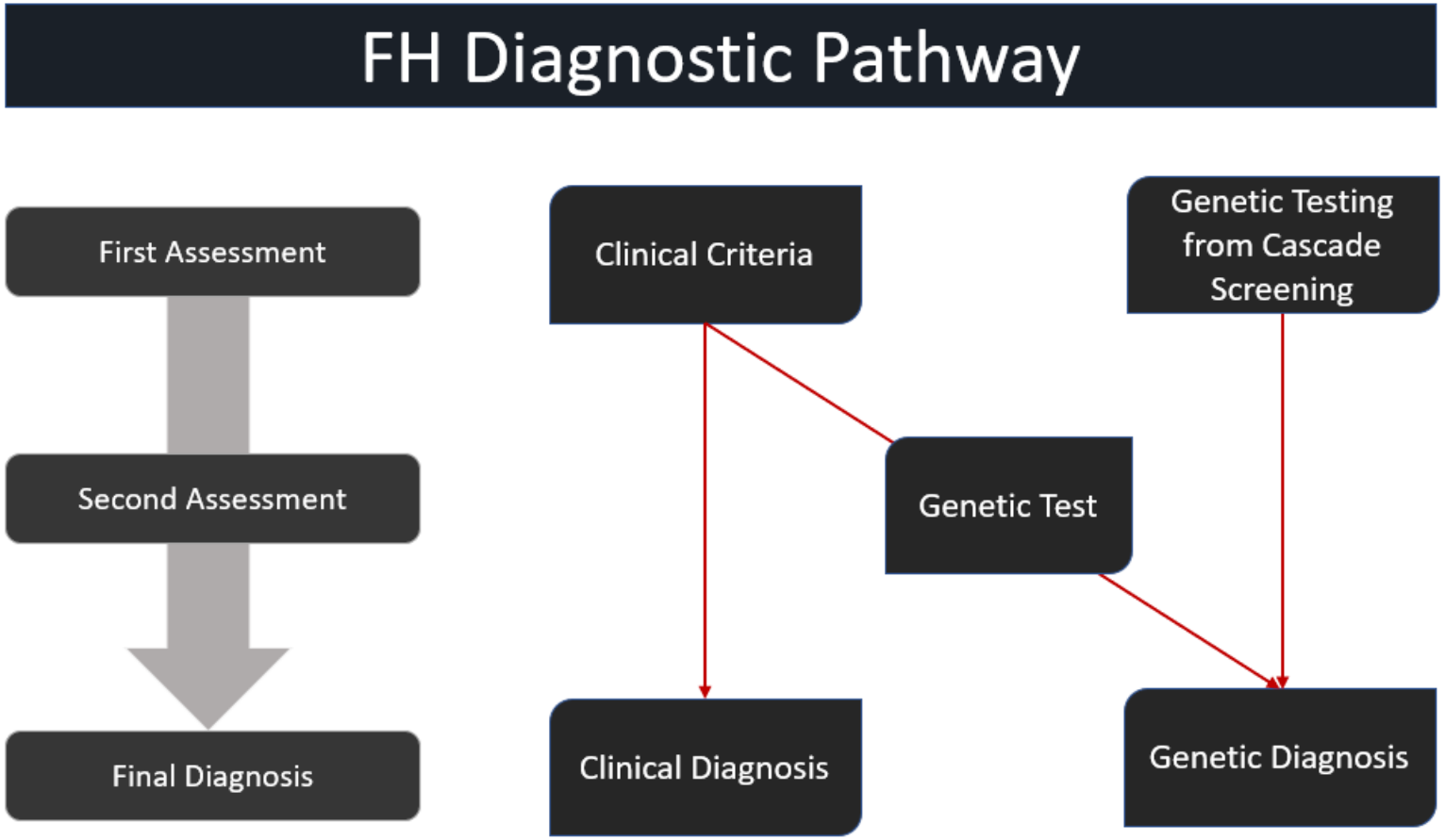
Supplementary Figure 1: Selection of children/adolescents with Heterozygous Familial Hypercholesterolaemia for inclusion in this study from the overall FHSC Registry

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



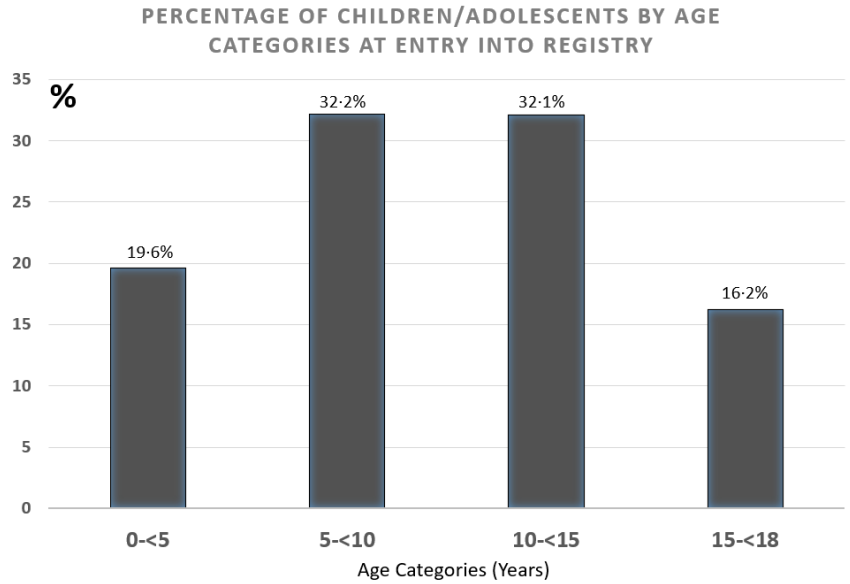
Supplemental Figure 2: Diagnostic process pathway considered for analysis

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.

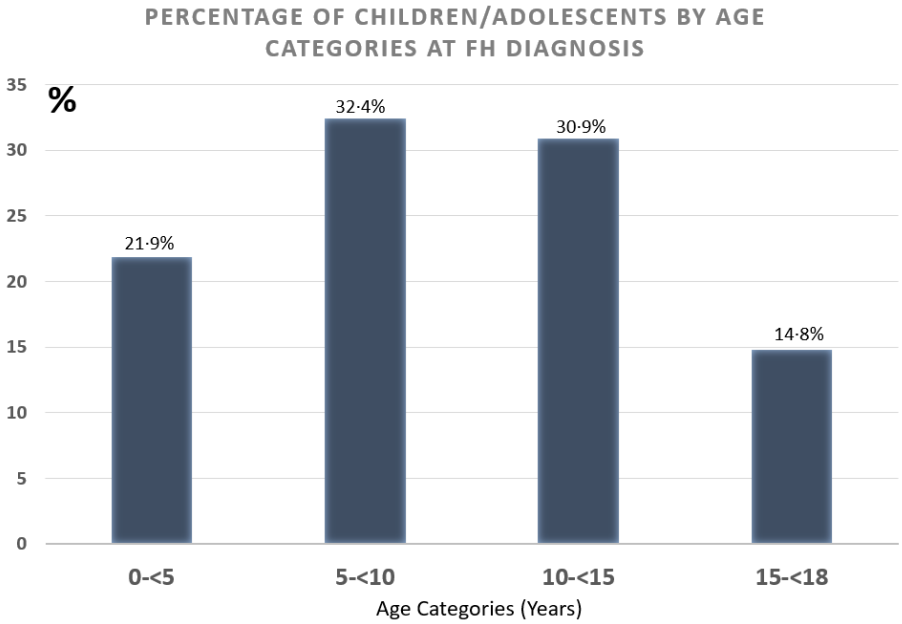


Supplementary Figure 3: Distribution of children and adolescents by age at registry entry and age at diagnosis of FH

Panel 3A: age at registry entry

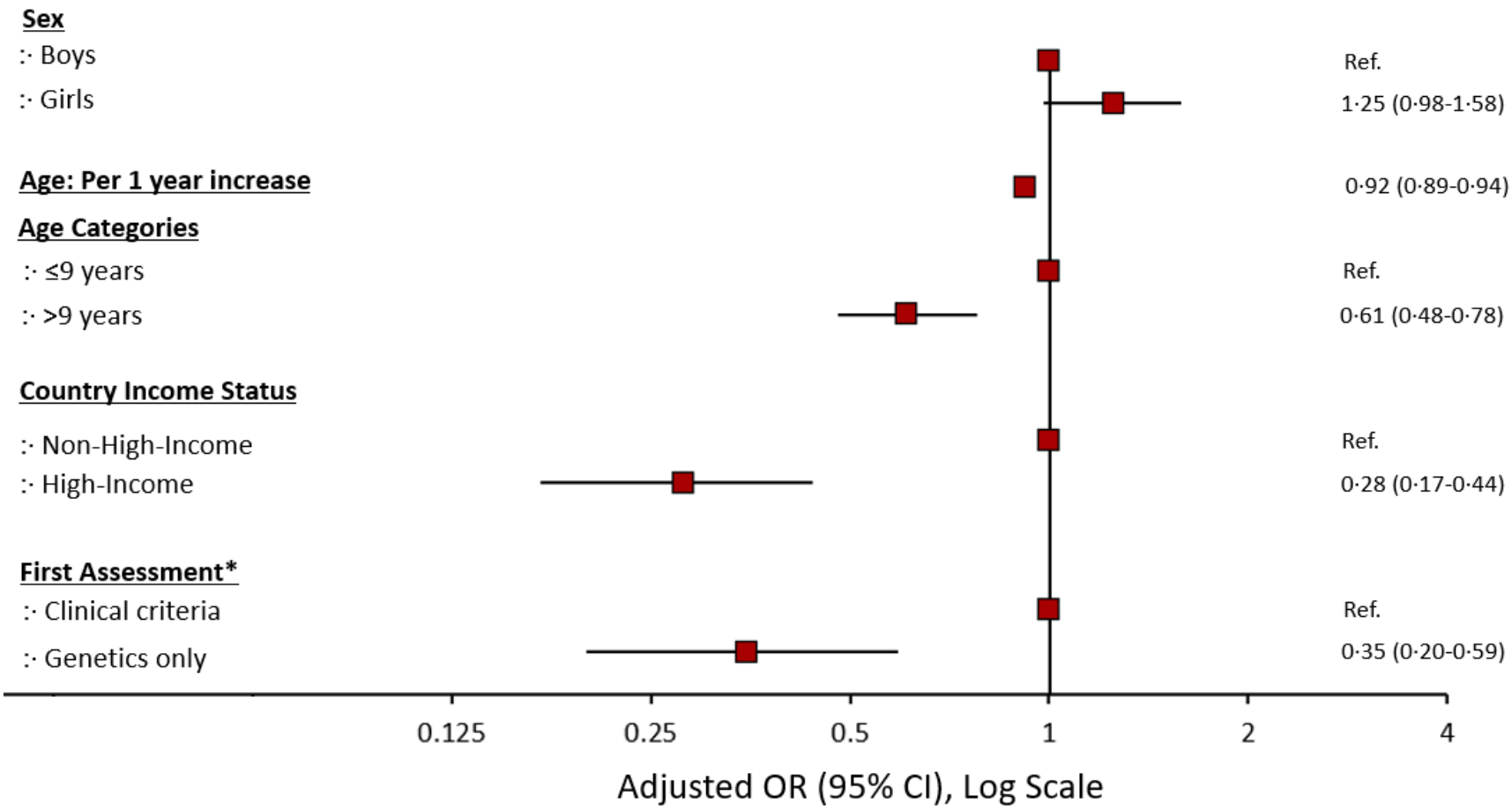


Panel 3B: age at FH diagnosis

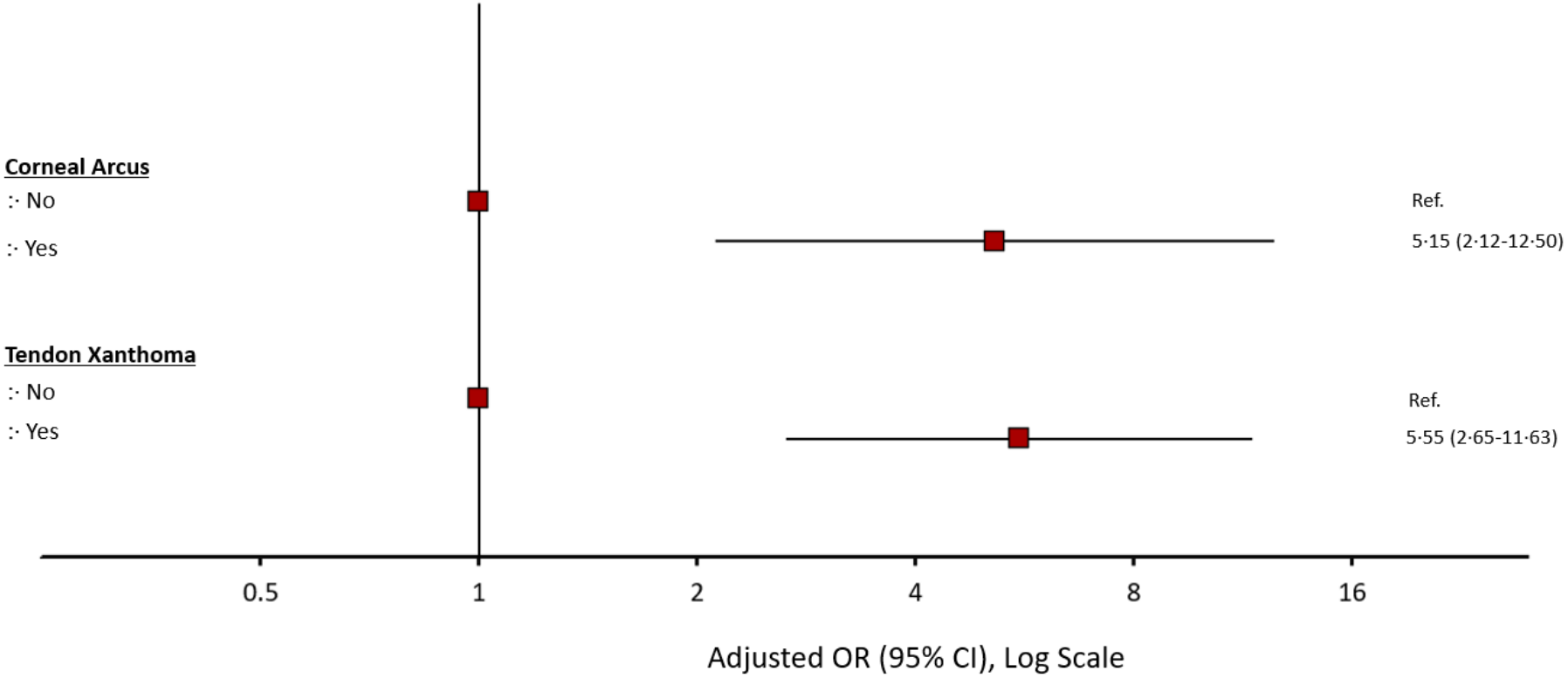


Supplemental Figure 4: Odds ratios for having an LDL-C >7.8 mmol/L amongst children and adolescents not on lipid-lowering medications (LLM)

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

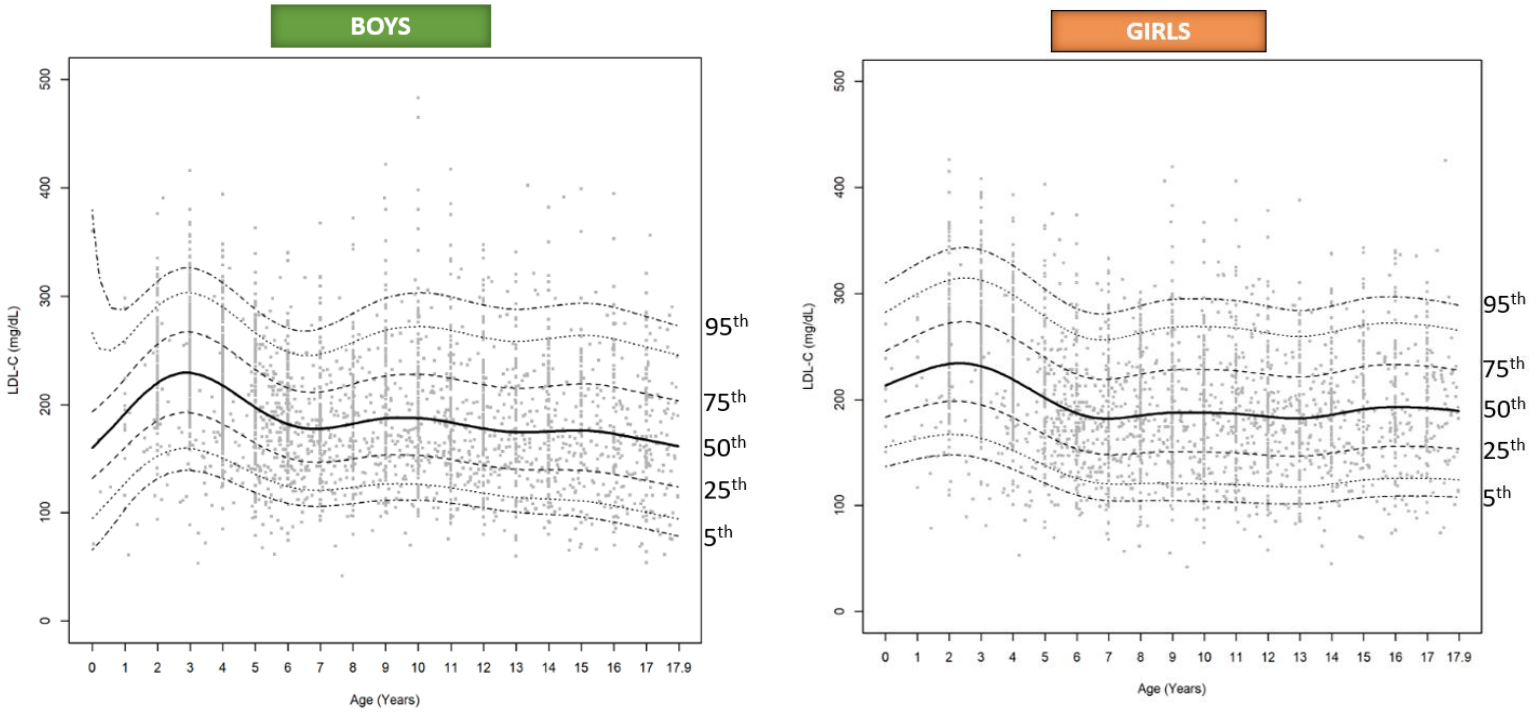


Panel 4B: Physical signs are adjusted by age and sex. Supplemental table 9 lists the numbers included in each sub-group alongside the unadjusted and adjusted odds ratios



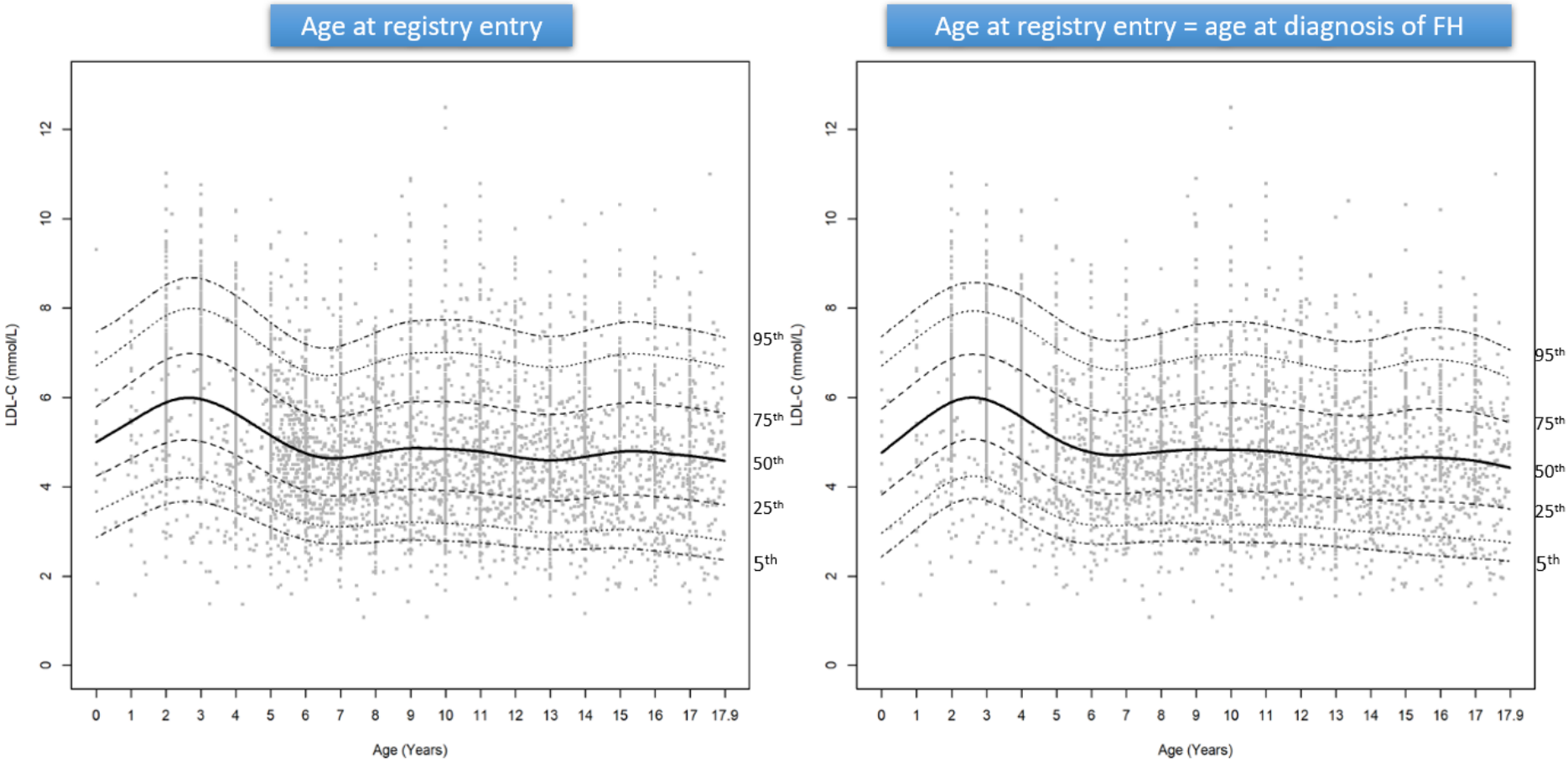
Supplemental Figure 5: Smooth percentile curves for LDL-C (mg/dL) by sex and age for children and adolescents at entry into registry and not on LLM

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



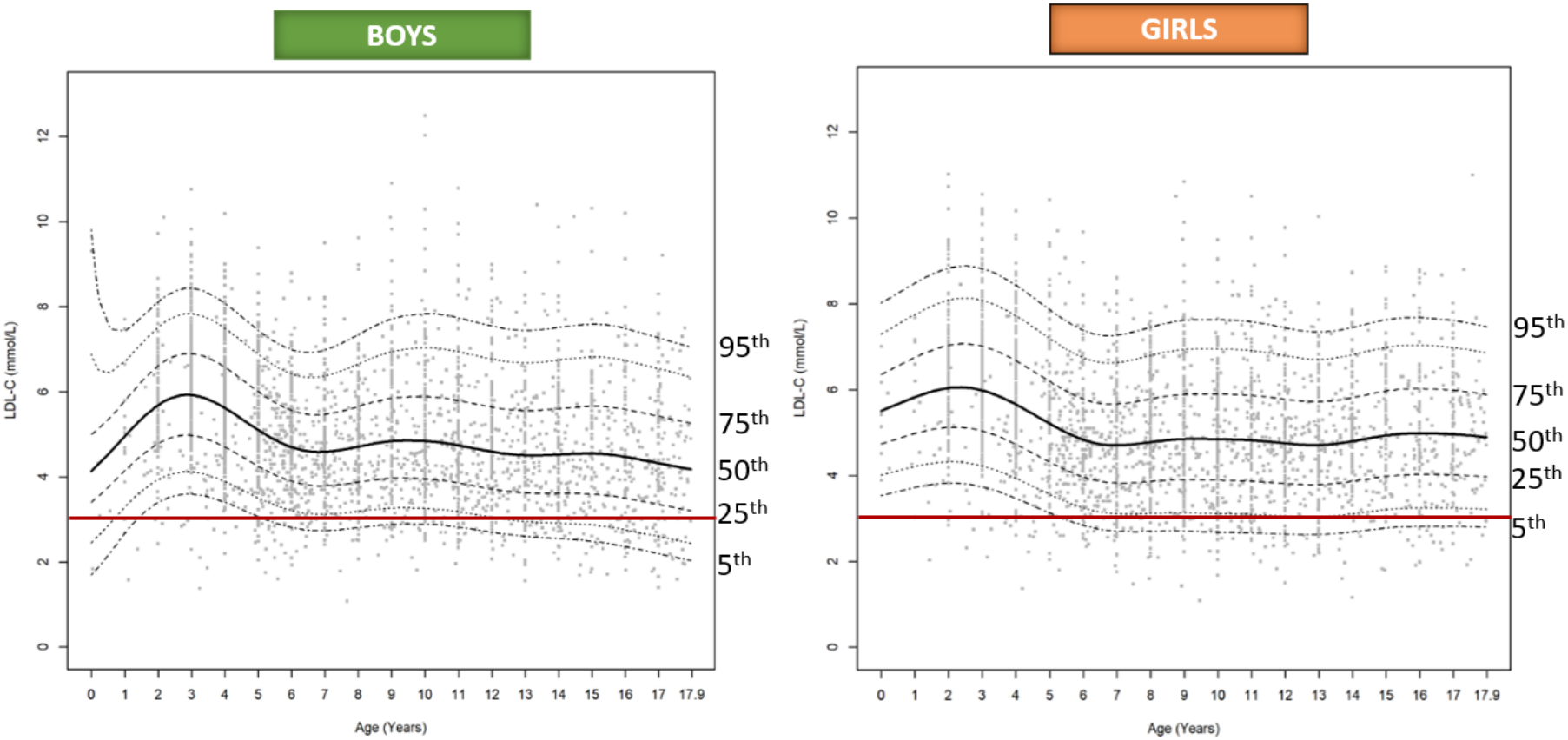
Supplementary Figure 6: Smooth percentile curves for LDL-C (mmol/L) showing age at entry into registry and age at FH diagnosis (where age at diagnosis of FH equals age at entry into registry) amongst children/adolescents not on LLM

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

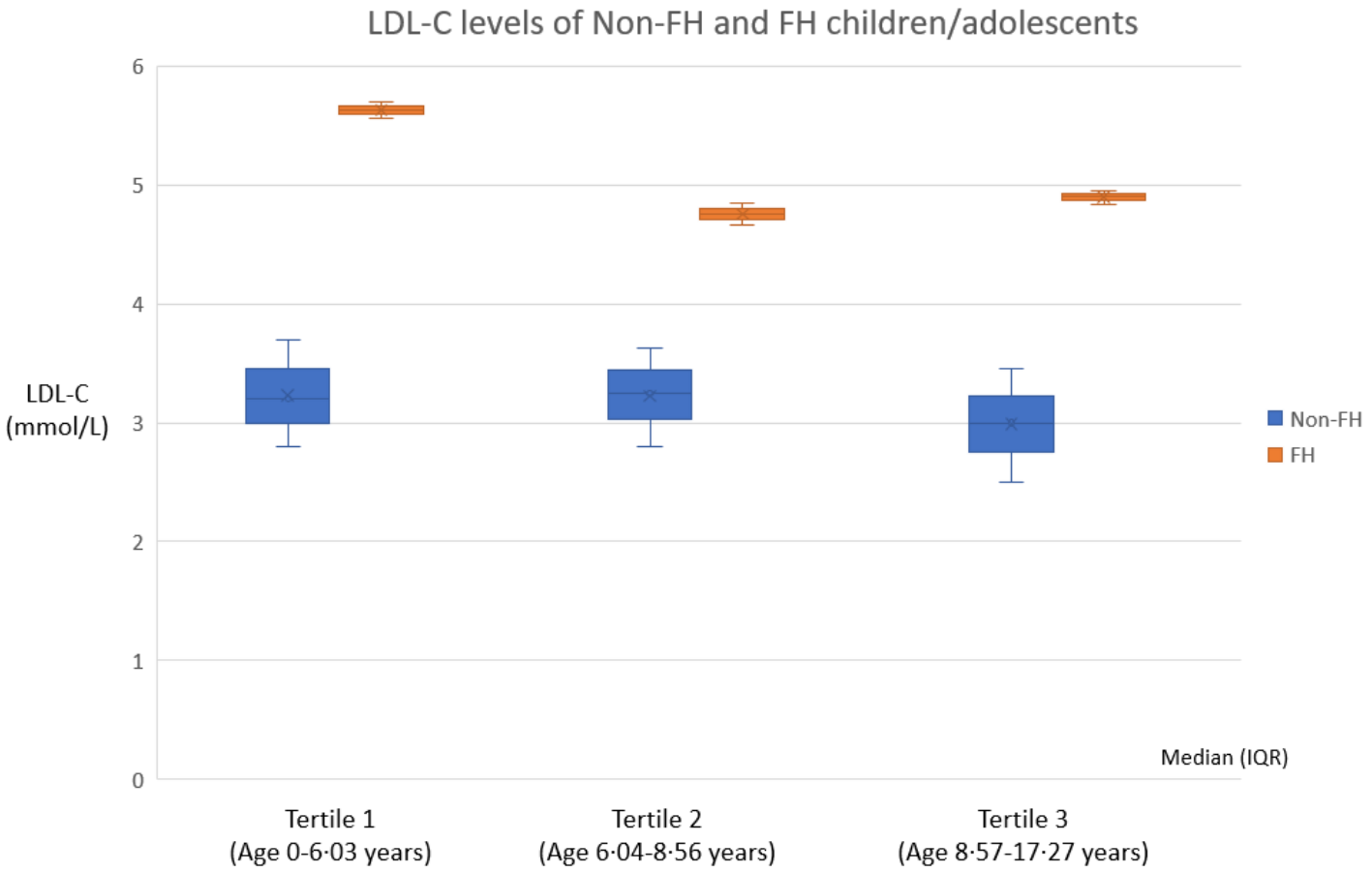


Supplemental Figure 7: Smoothed percentile curves for LDL-C (mmol/L) at entry into registry among children/adolescents not receiving lipid-lowering medication, with median LDL-C of non-FH individuals (horizontal red line)

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

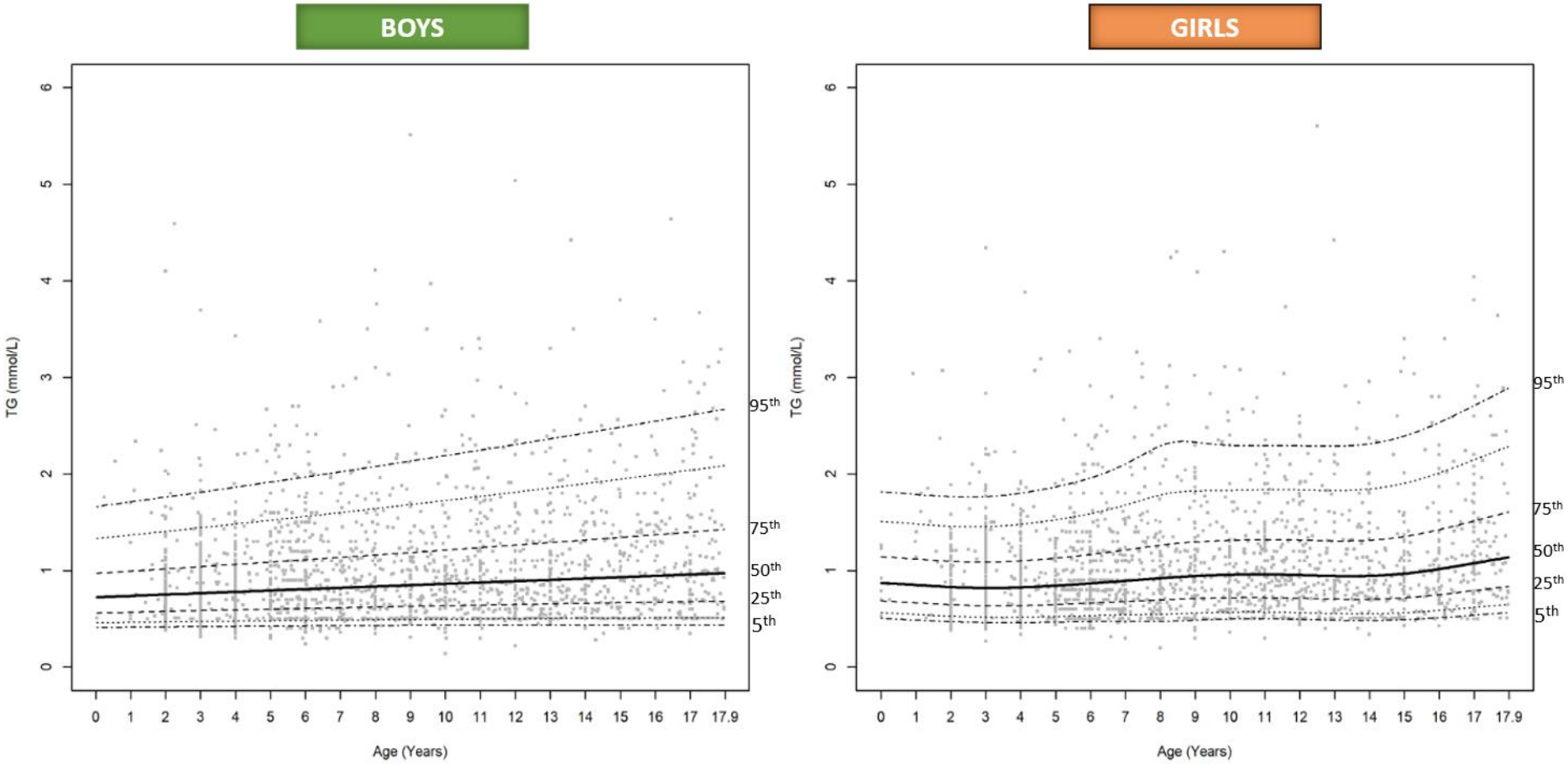


Supplemental Figure 8: Box and whisker plots showing LDL-C levels amongst non-FH and FH children and adolescents by tertiles of age at registry entry



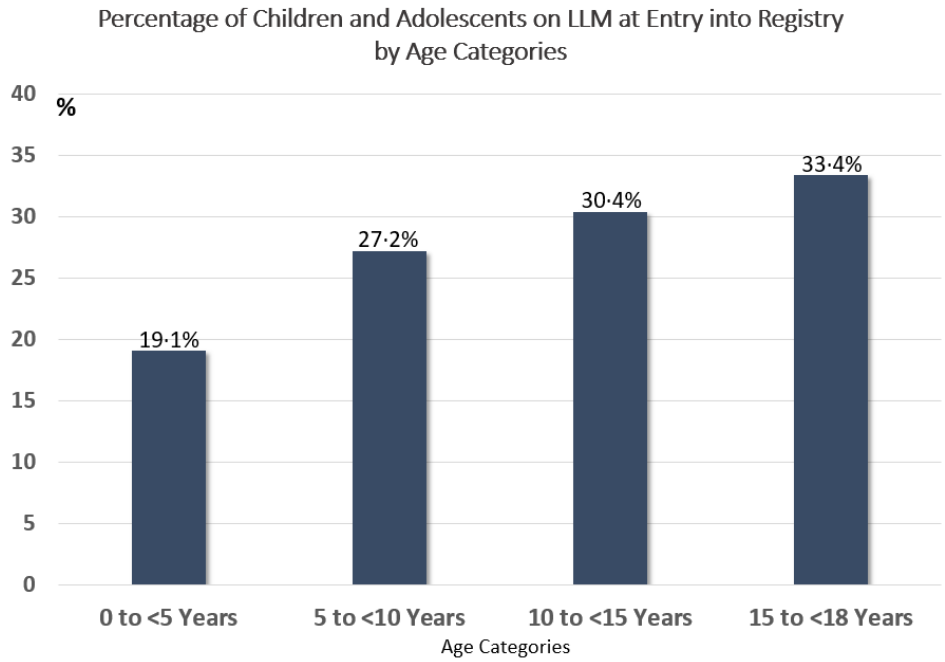
Supplementary Figure 9: Smooth percentile curves for triglyceride (mmol/L) levels at entry into the registry by sex and age amongst children/adolescent not on LLM

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

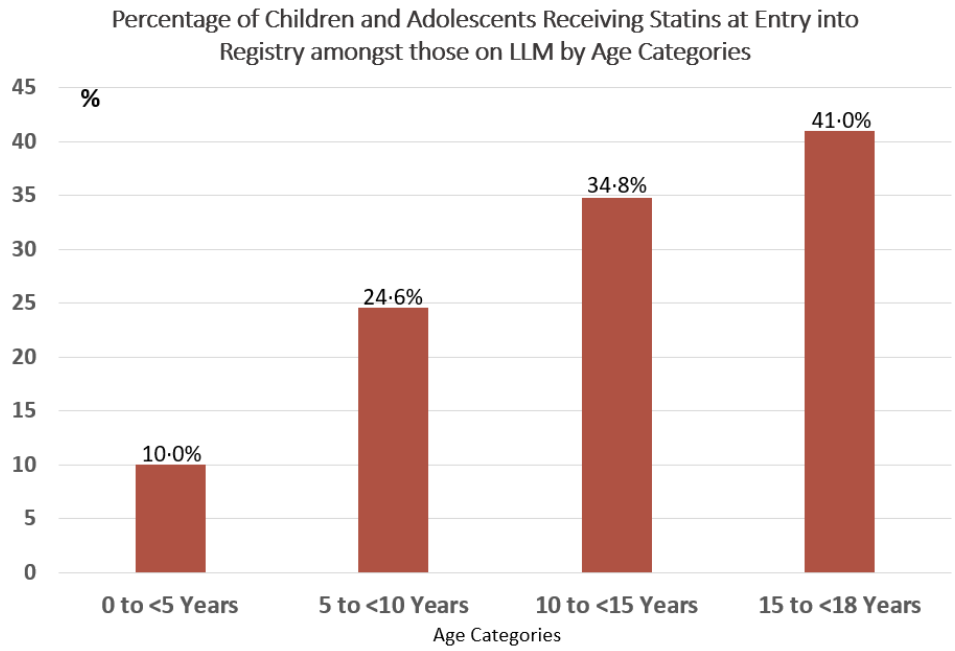


Supplemental Figure 10: Children and adolescents on lipid-lowering medication (LLM) at entry into registries

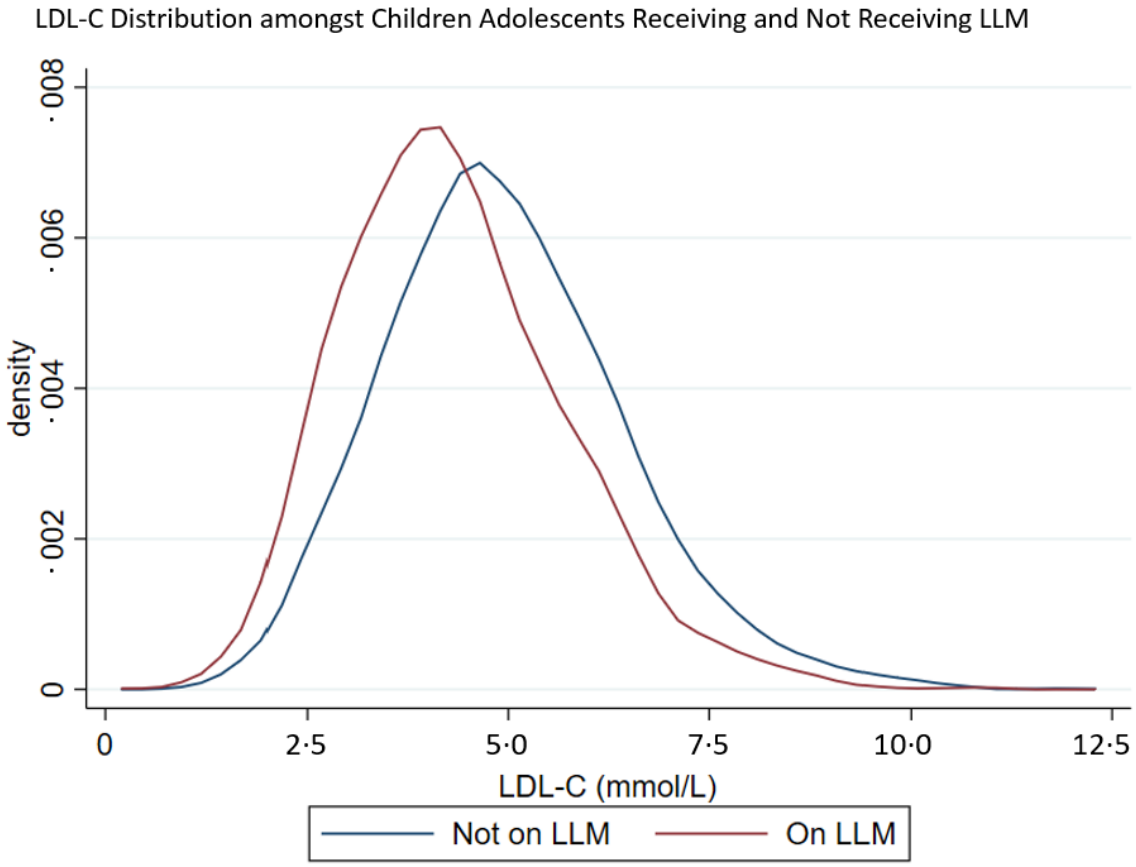
Panel 10A: Percentage of children/adolescents on lipid-lowering medication (LLM) at entry into registry by age categories



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.



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