Global perspective of familial hypercholesterolaemia: a cross-sectional study from the EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC)

*EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC)**

Summary

Background The European Atherosclerosis Society Familial Hypercholesterolaemia Studies Collaboration (FHSC) global registry provides a platform for the global surveillance of familial hypercholesterolaemia through harmonisation and pooling of multinational data. In this study, we aimed to characterise the adult population with heterozygous familial hypercholesterolaemia and described how it is detected and managed globally.

Methods Using FHSC global registry data, we did a cross-sectional assessment of adults (aged 18 years or older) with a clinical or genetic diagnosis of probable or definite heterozygous familial hypercholesterolaemia at the time they were entered into the registries. Data were assessed overall and by WHO regions, sex, and index versus non-index cases.

Findings Of the 61 612 individuals in the registry, 42 167 adults (21 999 [53·6%] women) from 56 countries were included in the study. Of these, 31 798 (75·4%) were diagnosed with the Dutch Lipid Clinic Network criteria, and 35 490 (84·2%) were from the WHO region of Europe. Median age of participants at entry in the registry was 46·2 years (IQR 34·3–58·0); median age at diagnosis of familial hypercholesterolaemia was 44·4 years (32·5–56·5), with 40·2% of participants younger than 40 years when diagnosed. Prevalence of cardiovascular risk factors increased progressively with age and varied by WHO region. Prevalence of coronary disease was 17·4% (2·1% for stroke and 5·2% for peripheral artery disease), increasing with concentrations of untreated LDL cholesterol, and was about two times lower in women than in men. Among patients receiving lipid-lowering medications, 16 803 (81·1%) were receiving statins and 3691 (21·2%) were on combination therapy, with greater use of more potent lipid-lowering medication in men than in women. Median LDL cholesterol was 5·43 mmol/L (IQR 4·32–6·72) among patients not taking lipid-lowering medications and 4·23 mmol/L (3·20–5·66) among those taking them. Among patients taking lipid-lowering medications, 2·7% had LDL cholesterol lower than 1·8 mmol/L; the use of combination therapy, particularly with three drugs and with proprotein convertase subtilisin–kexin type 9 inhibitors, was associated with a higher proportion and greater odds of having LDL cholesterol lower than 1·8 mmol/L. Compared with index cases, patients who were non-index cases were younger, with lower LDL cholesterol and lower prevalence of cardiovascular risk factors and cardiovascular diseases (all p<0·001).

Interpretation Familial hypercholesterolaemia is diagnosed late. Guideline-recommended LDL cholesterol concentrations are infrequently achieved with single-drug therapy. Cardiovascular risk factors and presence of coronary disease were lower among non-index cases, who were diagnosed earlier. Earlier detection and greater use of combination therapies are required to reduce the global burden of familial hypercholesterolaemia.

Funding Pfizer, Amgen, Merck Sharp & Dohme, Sanofi–Aventis, Daiichi Sankyo, and Regeneron.

Lancet 2021; 398: 1713–25

Published **Online** September 7, 2021 https://doi.org/10.1016/S0140-6736(21)01122-3

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Introduction

Recognition that familial hypercholesterolaemia is not an uncommon condition, whose clinical course can be improved through early detection and treatment, led to the 1998 WHO Report on familial hypercholesterolaemia,[1] which advocated the need to address the challenge of familial hypercholesterolaemia worldwide through multiple approaches. Since then, there has been insufficient progress in the implementation of key aspects of those recommendations, which include making an early diagnosis, providing effective treatment, and raising awareness.[2] Contemporary epidemiological and genetic studies now suggest that familial hypercholesterolaemia is approximately twice as common as previously thought, potentially affecting more than 25 million people worldwide.[3] Yet, with no consensus on approaches for detection or screening, fewer than 5% of individuals potentially affected are estimated to have been diagnosed, with scarce data from many world regions.[3,4]

Although different registries have been initiated in several countries to inform local policy independently, efforts to tackle the global burden of familial hypercholesterolaemia have been hampered by the lack of an

Research in context

Evidence before this study

We did a systematic search in PubMed for research articles published from inception to Feb 23, 2021, with no language restrictions. We included MeSH and free terms related to ("familial hypercholesterolaemia") and ("registry"/"gender"/"sex"/"index case"), or variations of these terms thereof. We screened articles by title and abstract to identify relevant studies. Reference lists of eligible articles were also searched for additional studies. Articles that explored familial hypercholesterolaemia and registries to characterise familial hypercholesterolaemia and its burden, identification, and management were considered. We also reviewed the most recent guidelines and consensus statements on dyslipidaemias and familial hypercholesterolaemia.

In 2020, large meta-analyses showed that familial hypercholesterolaemia is a relatively common inherited condition, affecting about one in 300 individuals in the general population (approximately twice the prevalence historically estimated). Information on prevalence and burden of familial hypercholesterolaemia is scarce in many countries and regions. Low rates (<5–10%) of familial hypercholesterolaemia identification are consistently reported. Beyond opportunistic screening, family cascade screening and universal screening have been proposed; however, there is no consensus on the optimal strategy, and screening programmes are not widely implemented, with only few exceptions. Characterisation of index cases versus non-index cases could help inform optimal strategies, but information reported is insufficient. Familial hypercholesterolaemia increases the risk of (premature) cardiovascular disease, particularly of coronary disease, with data suggesting that outcomes could be prevented through early identification and intervention. However, undertreatment is consistently reported. Sex disparities in identification and management of familial hypercholesterolaemia have been suggested, but this requires additional characterisation.

Added value of this study

The Familial Hypercholesterolaemia Studies Collaboration provides an integrated approach to assess the global burden of familial hypercholesterolaemia by bringing together multiple sources and registries, which are standardised, harmonised, and merged into a single global Registry. The study included over 42 000 adults with heterozygous familial hypercholesterolaemia from 56 countries. Although familial hypercholesterolaemia occurs across all WHO regions, some regional variations exist. Familial hypercholesterolaemia is detected late, on average when individuals are in their 40s, with only about 40% of cases diagnosed before age 40 years. Prevalence of cardiovascular disease and cardiovascular risk factors increased with age of diagnosis, suggesting that late diagnosis potentially misses out on opportunities to address other future determinants of health in addition to LDL cholesterol. However, for non-index cases, who appeared to be diagnosed at an earlier age than index cases, the prevalence of cardiovascular disease and risk factors was lower, supporting the role of screening from index cases. Only 2·7% of patients receiving lipid-lowering medications achieved LDL cholesterol lower than 1·8 mmol/L, with low use of combination therapy. Goal attainment improved incrementally with the number of therapies used, particularly when including PCSK9 inhibitors. We observed important differences by sex, with implications for screening and treatment.

Implications of all the available evidence

Identification of familial hypercholesterolaemia needs to be improved to detect individuals affected much earlier in their life course. Greater use of combination therapy is probably required to improve familial hypercholesterolaemia management and reduce the gap between guideline recommendations and clinical practice. This point raises challenges about accessibility and cost, particularly in low-income and middle-income countries. Sex disparities in familial hypercholesterolaemia detection and management seem to be present, with potential implications for care and outcomes.

integrated approach. The European Atherosclerosis Society (EAS) Familial Hypercholesterolaemia Studies Collaboration (FHSC)[5] was established to create a global registry of patients with familial hypercholesterolaemia, creating a network of investigators (currently from 66 countries worldwide) for the purpose of providing a platform for the global surveillance of familial hypercholesterolaemia through harmonisation and pooling of regional and national data. The FHSC aims to provide hitherto unavailable insights on the detection and management of familial hypercholesterolaemia on a global level, with potential implications for future public health strategies. In this study, we specifically aimed to characterise the adult population with heterozygous familial hypercholesterolaemia and describe how it is detected and managed globally.

See Online for appendix

Methods

Study design and population

The FHSC draws upon data from an international consortium of investigators with access to patients managed in specialist clinics that serve as national, regional, or local registries of familial hypercholesterolaemia. Individual data from these diverse sources are standardised to a common data dictionary, harmonised, and merged into a single global registry.[5] Additional details of methods and data management are described in the appendix (pp 15–18) and in the published protocol.[5]

The protocol and data governance of the registry (registered at ClinicalTrials.gov, NCT04272697) and its use for research have been approved by the Joint Research Compliance Office and Imperial College Research Ethics Committee (Imperial College London, London, UK). Investigators and organisations contributing to this registry were required to provide written confirmation that they comply with their local research and ethical policies and regulations for sharing data with the registry.

The registry consists of adults and children with a clinical or genetic diagnosis of homozygous or heterozygous familial hypercholesterolaemia; clinical diagnoses must conform with accepted clinical criteria (or modified criteria thereof), such as the Dutch Lipid Clinic Network (DLCN) criteria,[4] Make Early Diagnosis to Prevent Early Deaths (MEDPED),[5] Simon-Broome criteria,[6] Canadian definition of familial hypercholesterolaemia,[7] or Japanese Atherosclerosis Society familial hypercholesterolaemia criteria.[8] Individuals relying only on a self-reported history of familial hypercholesterolaemia and those with secondary causes of hypercholesterolaemia were excluded (additional details in the appendix pp 15–17). As of March 16, 2021, the registry includes more than 61 600 participants from 56 countries (of 66 countries formally in the FHSC network).

In our study, we did a cross-sectional assessment of adults (aged 18 years or older) with probable or definite heterozygous familial hypercholesterolaemia (possible and definite using Simon-Broome criteria) at the time they were entered into the registries. In individuals with a clinical (non-genetic) diagnosis, we excluded those with untreated LDL cholesterol of 12·9 mmol/L (500 mg/dL) or higher, because these concentrations make the presence of homozygous familial hypercholesterolaemia likely (either so-called true homozygous familial hypercholesterolaemia or compound or double heterozygotes).[9] Data were assessed overall (global) and by WHO regions,[10] sex, and index versus non-index cases. Index case was defined as the first documented familial hypercholesterolaemia case in a family; non-index cases were defined as relatives with familial hypercholesterolaemia identified through screening of the family from the index case (additional details in the appendix pp 15–16, 18).

Characteristics of individual registries and cohorts contributing to the FHSC registry are shown in the appendix (pp 26–33). Because the Netherlands contributed a large percentage of cases to the European region, we made separate analyses of this region for the Netherlands and for the European region excluding the Netherlands. Similarly, we did a sensitivity analysis for the overall FHSC cohort excluding the Netherlands. Due to the low number of cases from the WHO South-East Asia region, this region was considered together with the Western Pacific region.

Statistical analysis

We analysed merged data at individual level on the composite dataset. Where a specific country was not granted approval by its local ethical or research committee to provide individual-level data to the FHSC (the case of French Registry of Familial Hypercholesterolaemia), similar analyses to those done on the merged dataset were done by the corresponding investigator on their own individual-level dataset, and the aggregated results were shared with the FHSC.

Descriptive estimates are presented as mean (SD) or median (IQR), as appropriate, for continuous variables. Categorical variables are reported as absolute numbers and relative frequencies from the total number of participants with data available for the corresponding variable. No attempt was made to account for missing variables due to the descriptive nature of the analysis; data available for the variables included in the study are shown in the appendix (pp 34–35). We did between-group comparisons of continuous variables using independent-samples *t* test for normally distributed variables or Mann-Whitney *U* test for non-normally distributed variables; we used χ^2 test for categorical variables. Where appropriate, odds ratios (ORs) and 95% CIs were estimated with logistic regression to assess the association between a condition of interest and a certain exposure, adjusting for relevant variables. Tests were two-sided; statistical significance was defined as $p<0·05$. The analyses were done with IBM SPSS Statistics, version 27.

Role of the funding source

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

Results

Of the 61 612 individuals in the FHSC registry, 42 167 were aged 18 years or older with probable or definite heterozygous familial hypercholesterolaemia and were included in our study (appendix p 18). Most individuals (31 798 [75·4%]) were diagnosed with the DLCN criteria (either clinical criteria alone or both clinical and genetic criteria). Of the remaining individuals, 605 (1·4%) were diagnosed with Simon-Broome criteria and 2527 (6·0%) with MEDPED, 6563 (15·6%) were diagnosed with genetic criteria alone, and 674 (1·6%) were diagnosed with other diagnostic systems (appendix pp 26–33). Most individuals came from the WHO region of Europe: 35 490 (84·2%), including 19 529 (46·3%) from the Netherlands (table 1). In the African region, 839 (99·4%) of 844 individuals were from South Africa, with the remaining coming from Nigeria.

Median age of participants at entry in the registry was 46·2 years (IQR 34·3–58·0) and 21 999 (53·6%) were women (table 1). Age at which familial

	Overall cohort	Overall cohort excluding the Netherlands	By WHO region					
			Africa*	Americas	Eastern Mediterranean	Europe excluding the Netherlands	The Netherlands	South-East Asia and Western Pacific
Total number	42 167	22 638	844 (2·0%)	3262 (7·7%)	392 (0·9%)	15 961 (37·9%)	19 529 (46·3%)	2179 (5·2%)
Sex								
Men	19 031 (46·4%)	10 000 (46·5%)	370 (43·8%)	1352 (45·3%)	216 (55·1%)	6981 (46·2%)	9031 (46·2%)	1081 (49·6%)
Women	21 999 (53·6%)	11 501 (53·5%)	474 (56·2%)	1631 (54·7%)	176 (44·9%)	8123 (53·8%)	10 498 (53·8%)	1097 (50·4%)
Age at registry entry, years	46·2 (34·3–58·0)	48·0 (36·0–59·0)	40·0 (32·4–50·0)	46·0 (35·0–58·0)	43·8 (35·0–52·0)	49·0 (37·0–59·8)	44·4 (32·8–57·5)	50·0 (38·7–59·0)
Age at FH diagnosis, years	44·4 (32·5–56·5)	44·4 (32·0–55·0)	··†	46·0 (33·9–58·0)	43·6 (34·0–52·5)	43·0 (30·0–54·1)	44·4 (32·8–57·5)	48·2 (36·0–57·0)
Hypertension	7030 (19·2%)	5146 (30·2%)	130 (15·4%)	538 (23·0%)	74 (23·0%)	3816 (33·3%)	1884 (9·6%)	588 (28·0%)
Diabetes	1843 (5·0%)	1372 (8·0%)	11 (1·3%)	188 (7·8%)	86 (26·5%)	858 (7·4%)	471 (2·4%)	229 (11·2%)
Body-mass index, kg/m²	25·1 (22·5–28·2)	25·9 (23·1–29·3)	··†	25·7 (23·0–29·0)	29·1 (25·9–33·0)	26·1 (23·3–29·4)	24·5 (22·1–27·3)	25·2 (22·5–28·3)
Smoking	8844 (23·5%)	3822 (21·0%)	180 (21·5%)	414 (18·1%)	50 (19·1%)	2860 (22·0%)	5022 (25·9%)	318 (17·3%)
CAD	6057 (17·4%)	4334 (28·2%)	292 (34·6%)	413 (19·5%)	··‡	3152 (30·4%)	1723 (8·8%)	467 (23·9%)
Premature CAD	4031 (11·3%)	3284 (20·5%)	244 (30·0%)	72 (14·9%)	77 (30·1%)	2488 (20·0%)	747 (3·8%)	403 (20·2%)
Stroke	704 (2·1%)	426 (3·2%)	32 (3·8%)	30 (2·2%)	··‡	324 (3·4%)	278 (1·4%)	40 (2·2%)
Peripheral artery disease	636 (5·2%)§	636 (5·2%)§	21 (2·5%)	29 (2·2%)	··‡	567 (6·8%)	··§	18 (1·1%)
LLM	23 175 (59·5%)	12 902 (66·4%)	533 (65·9%)	1698 (72·0%)	301 (80·3%)	9216 (63·7%)	10 273 (52·6%)	1154 (80·6%)
Total cholesterol, mmol/L								
Participants not on LLM	7·45 (6·15–8·86)	8·35 (7·32–9·65)	9·30 (8·20–10·85)	8·10 (7·10–9·18)	8·10 (7·60–10·20)	8·37 (7·37–9·65)	6·23 (5·36–7·21)	7·39 (6·50–8·43)
Participants on LLM	6·15 (5·08–7·80)	6·98 (5·37–8·60)	6·93 (5·10–8·10)	8·40 (7·09–9·80)	7·50 (6·10–8·93)	6·67 (5·21–8·38)	5·61 (4·86–6·60)	6·01 (4·81–7·58)
LDL cholesterol, mmol/L								
Participants not on LLM	5·43 (4·32–6·72)	6·30 (5·23–7·55)	7·70 (6·50–8·95)	6·07 (5·14–7·00)	7·09 (5·48–8·40)	6·26 (5·22–7·43)	4·43 (3·61–5·32)	5·30 (4·40–6·52)
Participants on LLM	4·23 (3·20–5·66)	4·84 (3·39–6·30)	5·09 (4·10–6·13)	5·75 (4·40–7·21)	6·07 (4·65–7·37)	4·58 (3·21–6·15)	3·80 (3·09–4·74)	4·35 (3·00–5·50)
HDL cholesterol, mmol/L								
Participants not on LLM	1·25 (1·01–1·53)	1·32 (1·10–1·60)	1·10 (0·90–1·40)	1·20 (1·00–1·45)	1·15 (0·96–1·40)	1·37 (1·13–1·66)	1·15 (0·92–1·42)	1·32 (1·10–1·60)
Participants on LLM	1·23 (1·00–1·50)	1·29 (1·06–1·58)	1·20 (0·94–1·42)	1·14 (0·91–1·40)	1·12 (0·91–1·32)	1·34 (1·11–1·63)	1·16 (0·93–1·42)	1·30 (1·10–1·60)
Triglycerides, mmol/L								
Participants not on LLM	1·28 (0·88–1·89)	1·35 (0·96–1·98)	1·30 (0·90–1·80)	1·30 (0·94–1·90)	1·43 (1·10–1·86)	1·35 (0·94–1·98)	1·17 (0·78–1·76)	1·41 (1·00–1·92)
Participants on LLM	1·24 (0·85–1·82)	1·31 (0·90–1·93)	1·20 (0·82–1·80)	1·50 (1·07–2·20)	1·63 (1·10–2·36)	1·28 (0·90–1·86)	1·14 (0·78–1·70)	1·30 (0·90–1·85)

Data are n (%) or median (IQR). Data available for the variables included in the study are shown in the appendix (pp 34–35). CAD=coronary artery disease. FH=familial hypercholesterolaemia. LLM=lipid-lowering medication. *For the Africa region, most cases (839 [99·4%]) were from South Africa, with the remaining cases from Nigeria. †Age at FH diagnosis and body-mass index data not available in most cases from the region of Africa. ‡Data not available in most datasets (primarily collected premature disease, instead of overall disease). §Information on peripheral artery disease was not available in the dataset from the Netherlands.

***Table 1:* Characteristics of FH patients overall and stratified by geographical region**

hypercholesterolaemia was diagnosed was known in 30 560 participants and was a median of 44·4 years (32·5–56·5; 12 257 [40·2%] diagnosed before age 40 years and 626 [2·1%] diagnosed before age 18 years; figure 1, appendix p 19). 7030 (19·2%) participants had hypertension, 1843 (5·0%) had diabetes, and 15 318 (50·1%) had a body-mass index (BMI) of 25 kg/m² or higher (table 1, figure 2). The prevalence of cardiovascular risk factors increased progressively with age (figure 2; appendix p 20) and varied by region (table 1). We observed a higher prevalence of hypertension in Europe (excluding the Netherlands) and a higher prevalence of diabetes and higher BMI in the Eastern Mediterranean region. By comparison, a lower prevalence of these cardiovascular risk factors was observed in the Dutch cohort.

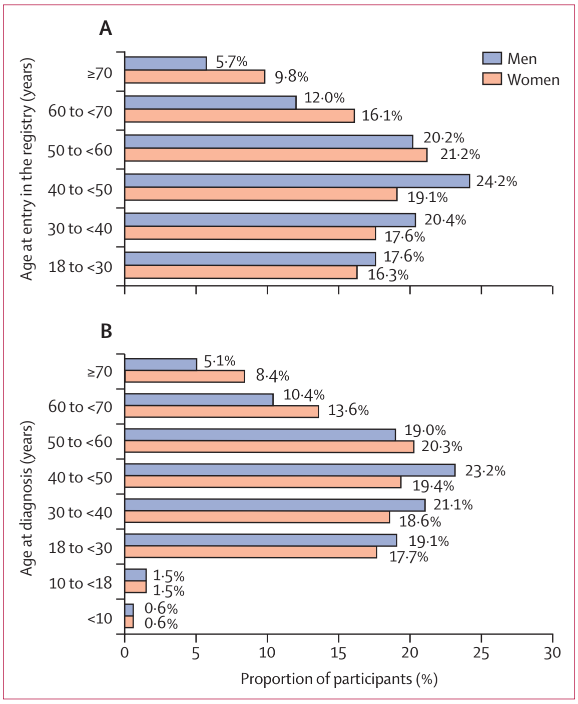

***Figure 1*: Distribution of participants by age and sex at entry in the registry (A) and at the time of familial hypercholesterolaemia diagnosis (B)**
Inclusion criteria for the study was age 18 years or older at entry in the registry.

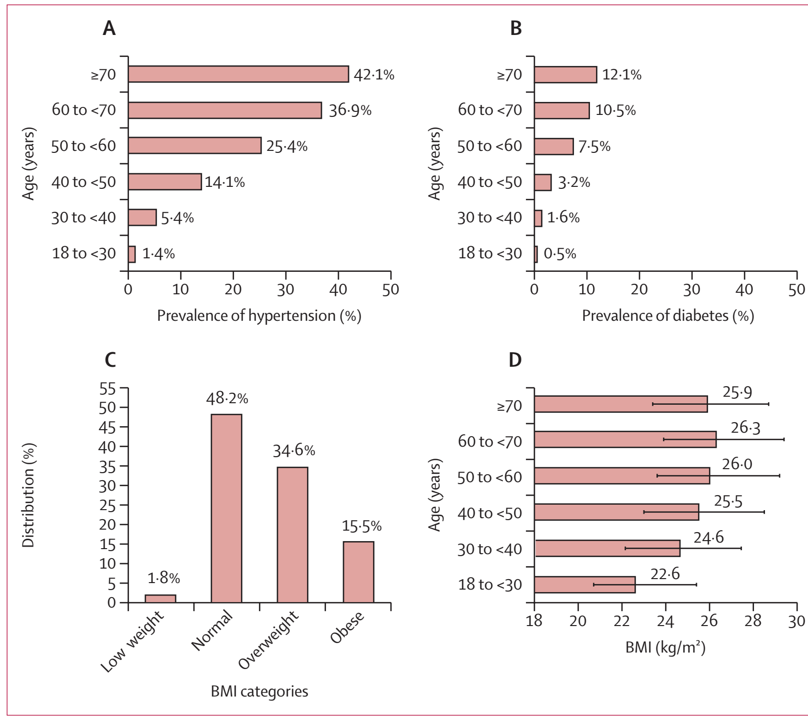

***Figure 2*: Prevalence of hypertension (A) and diabetes (B) by age and distribution of BMI overall (C) and by age (D)**
(C) Low weight indicates BMI lower than 18·5 kg/m², normal weight indicates BMI from 18·5 to lower than 25 kg/m², overweight indicates BMI from 25 to lower than 30 kg/m², and obesity indicates BMI of 30 kg/m² or higher. (D) Data are median and error bars represent the IQR. BMI=body-mass index.

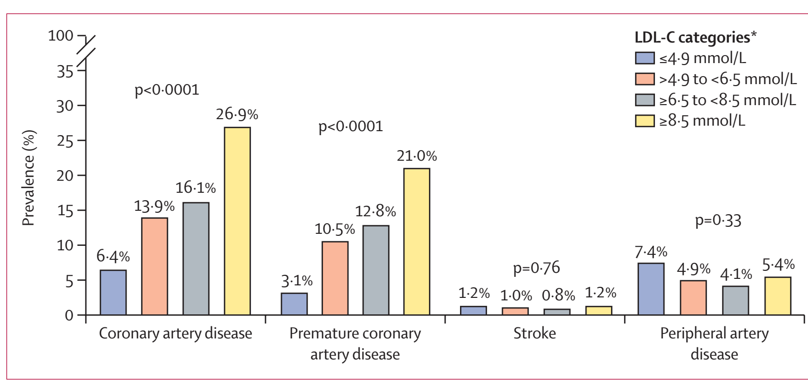

***Figure 3*: Cardiovascular disease by LDL-C concentrations among patients not receiving lipid-lowering medication**
The p values are for the comparison across LDL-C categories within each cardiovascular disease group. LDL-C=LDL cholesterol. *LDL-C cutoffs are based on the categories of LDL-C in the Dutch Lipid Clinic Network familial hypercholesterolaemia diagnostic criteria.

Coronary artery disease (CAD) was the most prevalent type of cardiovascular disease (table 1). Prevalence of premature CAD (occurring in men younger than 55 years and women younger than 60 years) was 11·3% (4031 participants). The prevalence of CAD increased progressively with increasing concentrations of untreated LDL cholesterol (p<0·0001), unlike stroke and peripheral artery disease, for which prevalences did not vary significantly across LDL cholesterol concentrations (figure 3). The Dutch cohort had lower prevalences of CAD and stroke than those overall and those in the European region excluding the Netherlands (table 1).

Women were, on average, approximately 2·5 years older than men at the time of diagnosis (table 2), with 6332 (38·4%) women diagnosed before age 40 years versus 5892 (42·3%) men (figure 1). Prevalence of CAD was about two-times lower in women than in men (p<0·0001; figure 4A). After adjusting for age, baseline characteristics, lipid concentrations, and lipid-lowering medications, women had significantly lower odds of having CAD than men (figure 4B). We found no significant differences by sex in the prevalence of stroke or peripheral artery disease (figure 4; appendix p 37).

At the time of study entry, 23 175 (59·5%) patients were taking lipid-lowering medications (figure 5; appendix p 38). Among patients taking lipid-lowering medications, 16 803 (81·1%) were taking statins, with or without other lipid-lowering medications (figure 5A; appendix p 39). These percentages were similar for both sexes (p=0·60, appendix p 21); however, more men (1245 [16·6%]) than women (1103 [13·1%]) were on the highest statin doses (atorvastatin 80 mg per day or rosuvastatin 40 mg per day; p<0·001; appendix p 40). The proportions of men taking ezetimibe or proprotein convertase subtilisin–kexin type 9 inhibitors (PCSK9i; with or without any other lipid-lowering medication) were higher than those of women (both p≤0·0002; appendix p 21). Overall, 21·2% of patients were on combination therapy with two

	Patients stratified by sex				Patients stratified by index case status			
	Men	Women	Mean difference (95% CI)	p value	Index cases	Non-index cases	Mean difference (95% CI)	p value
Patients	16 890 (45·8%)	19 945 (54·1%)	NA	NA	8718 (32·6%)	18 017 (67·4%)	NA	NA
Sex	..	..	..	..	..	..	..	..
Men	..	..	..	..	3928 (45·4%)	8300 (46·6%)	NA	..
Women	..	..	..	..	4725 (54·6%)	9498 (53·4%)	NA	0·058
Age at registry entry, years	44·9 (34·0 to 55·8)	48·2 (35·0 to 60·0)	−2·9 (−3·2 to −2·6)	<0·0001	50·0 (39·0 to 59·8)	44·0 (32·1 to 57·7)	3·8 (3·4 to 4·2)	<0·0001
Age at FH diagnosis, years	43·0 (32·0 to 54·4)	46·0 (33·0 to 58·3)	−2·5 (−2·8 to −2·1)	<0·0001	47·8 (36·5 to 57·1)	43·6 (31·6 to 57·1)	1·8 (1·4 to 2·2)	<0·0001
Hypertension	2554 (17·2%)	3375 (19·1%)	NA	<0·0001	1773 (21·1%)	2284 (12·8%)	NA	<0·0001
Diabetes	755 (5·1%)	887 (5·0%)	NA	0·79	499 (5·9%)	609 (3·4%)	NA	<0·0001
Body-mass index, kg/m²	25·6 (23·3 to 28·4)	24·6 (22·0 to 28·1)	0·5 (0·4 to 0·7)	<0·0001	26·0 (23·3 to 29·2)	24·6 (22·1 to 27·4)	1·5 (1·3 to 1·6)	<0·0001
Smoking	4347 (28·4%)	3734 (20·4%)	NA	<0·0001	1036 (12·7%)	5199 (29·4%)	NA	<0·0001
LLM	9646 (61·1%)	10 916 (58·4%)	NA	<0·001	3869 (49·1%)	10 739 (60·9%)	NA	<0·0001
Total cholesterol, mmol/L	..	..	..	..	..	..	..	..
Participants not on LLM	7·20 (5·97 to 8·60)	7·60 (6·30 to 9·01)	−0·39 (−0·49 to −10·9)	<0·0001	8·20 (7·16 to 9·56)	6·44 (5·50 to 7·46)	1·81 (1·65 to 1·96)	<0·0001
Participants taking LLM	5·96 (4·90 to 7·55)	6·29 (5·20 to 8·00)	−0·37 (−0·43 to −0·31)	<0·0001	6·54 (5·07 to 8·20)	5·71 (4·93 to 6·81)	0·76 (0·68 to 0·85)	<0·0001
LDL cholesterol, mmol/L	..	..	..	..	..	..	..	..
Participants not on LLM	5·35 (4·22 to 6·61)	5·50 (4·40 to 6·84)	−0·19 (−0·28 to −0·09)	<0·0002	6·06 (5·04 to 7·40)	4·62 (3·72 to 5·54)	1·51 (1·36 to 1·66)	<0·0001
Participants taking LLM	4·18 (3·16 to 5·51)	4·26 (3·24 to 5·75)	−0·14 (−0·20 to −0·09)	<0·0001	4·68 (3·22 to 6·10)	3·89 (3·12 to 4·93)	0·65 (0·57 to 0·73)	<0·0001
HDL cholesterol, mmol/L	..	..	..	..	..	..	..	..
Participants not on LLM	1·10 (0·91 to 1·32)	1·39 (1·14 to 1·68)	−0·29 (−0·32 to −0·27)	<0·0001	1·37 (1·14 to 1·66)	1·18 (0·95 to 1·47)	0·21 (0·17 to 0·24)	<0·0001
Participants taking LLM	1·10 (0·90 to 1·32)	1·37 (1·12 to 1·64)	−0·28 (−0·30 to −0·27)	<0·0001	1·29 (1·08 to 1·60)	1·17 (0·95 to 1·43)	0·15 (0·13 to 0·17)	<0·0001
Triglycerides, mmol/L	..	..	..	..	..	..	..	..
Participants not on LLM	1·39 (0·96 to 2·07)	1·19 (0·82 to 1·73)	0·30 (0·24 to 0·36)	<0·0001	1·33 (1·00 to 1·94)	1·19 (0·80 to 1·76)	0·10 (0·02 to 0·17)	<0·0001
Participants taking LLM	1·32 (0·90 to 1·99)	1·16 (0·81 to 1·70)	0·28 (0·24 to 0·33)	<0·0001	1·40 (0·98 to 1·99)	1·16 (0·79 to 1·71)	0·27 (0·21 to 0·33)	<0·0001

Data are n (%) or median (IQR), unless otherwise specified. Information on index or non-index case available for 26 735 patients. Information on patients stratified by sex does not include data from France (aggregated data by sex not available). FH=familial hypercholesterolaemia. LLM=lipid-lowering medication. NA=not applicable.

***Table 2:* Characteristics of patients with FH stratified by sex and by index case status**

or three of statins, ezetimibe, or PCSK9i (1871 [22·7%] men and 1818 [19·9%] women, p<0·0001; figure 5B, appendix pp 21, 41).

Lipid concentrations, stratified by patients taking or not taking lipid-lowering medications, are shown in table 1 and the appendix (p 42). LDL cholesterol concentrations were broadly similar between men and women when considering the overall cohort (table 2); however, when stratified by age 50 years (broadly accounting for pre-menopause and post-menopause in women), LDL cholesterol among those not on lipid-lowering medications were significantly higher among women aged 50 years or older compared with that of men above the same age (median 5·93 mmol/L, IQR 4·86–7·17, in women *vs* 5·20 mmol/L, 4·19–6·40, in men; mean difference 0·64 mmol/L, 95% CI 0·46–0·82, p<0·0001). We found no significant differences in LDL cholesterol concentrations by sex in patients younger than 50 years (p=0·31, appendix p 43). Differences in lipid-lowering medication and prevalence of cardiovascular disease in women by age of 50 years are shown in appendix p 44.

Among patients taking statins, ezetimibe, or PCSK9i, 308 (2·7%) had LDL cholesterol lower than 1·8 mmol/L at entry in the registry (figure 6A); this percentage was lower for women (123 [2·0%]) than for men (185 [3·4%]; p<0·0001; appendix p 22). After adjusting for age, baseline characteristics, and type of lipid-lowering medication, the odds of having LDL cholesterol lower than 1·8 mmol/L were lower for women than for men (OR 0·63, 95% CI 0·48–0·82; p=0·0007; appendix p 22). The use of combination therapy was associated with a

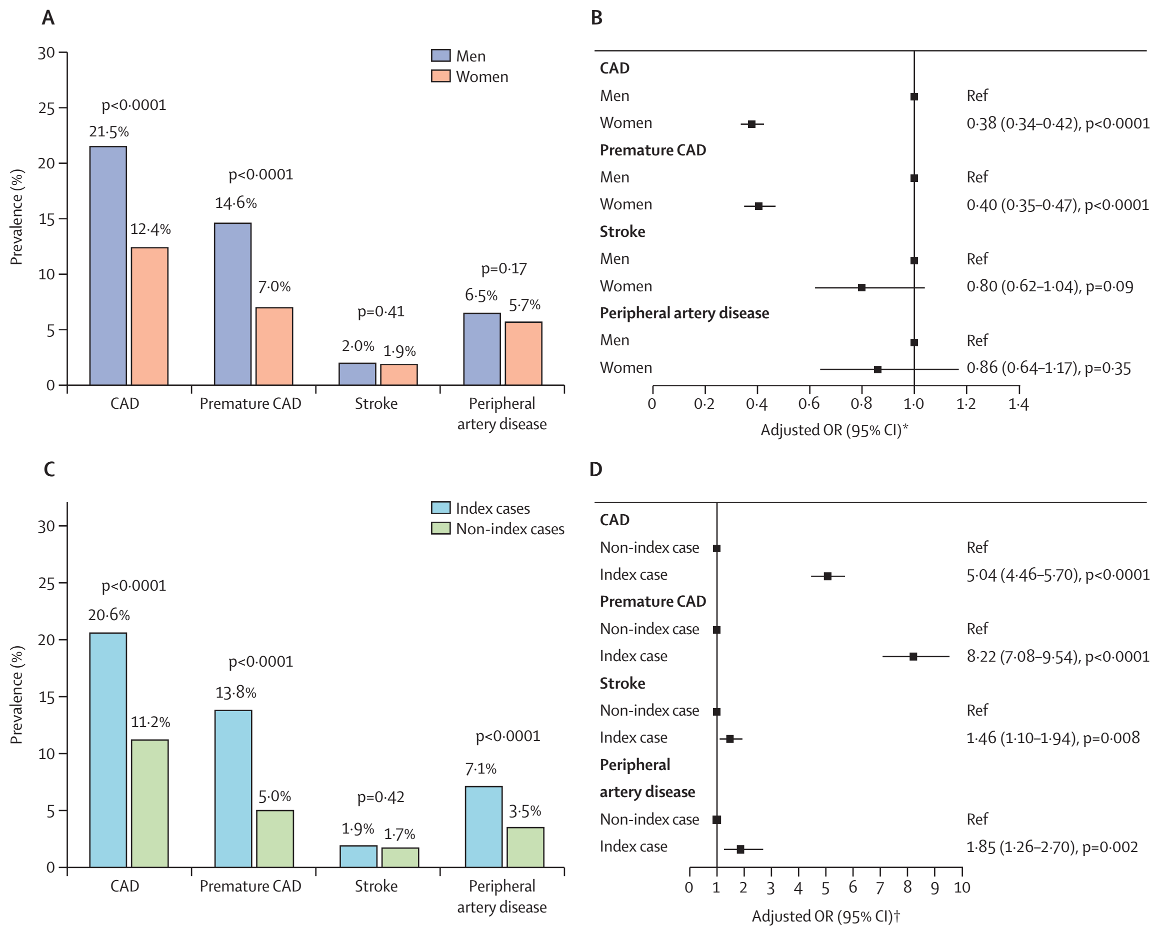

***Figure 4*: Cardiovascular disease stratified by sex (A, B) and by index case status (C, D)**
Panels show prevalence of type of cardiovascular disease stratified by sex (A), association of sex with type of cardiovascular disease (B), prevalence of cardiovascular disease among index and non-index cases (C), and association of index and non-index cases with cardiovascular disease (D). CAD=coronary artery disease. HDL-C=HDL cholesterol. LDL-C=LDL cholesterol. OR=odds ratio. *ORs adjusted by age, baseline comorbidities (hypertension, diabetes, smoking, and body-mass index), lipid levels (LDL-C, HDL-C, and log[triglycerides]), lipid-lowering medication, index case, and interaction between LDL-C and lipid-lowering medication. †ORs adjusted by age, sex, baseline comorbidities (hypertension, diabetes, smoking, and body-mass index), lipid levels (LDL-C, HDL-C, and log[triglycerides]), lipid-lowering medication, and interaction between LDL-C and lipid-lowering medication.

higher proportion and greater odds of having LDL cholesterol lower than 1·8 mmol/L, particularly with the combination of three drugs and when using PCSK9i (figure 6B–D). Similar patterns were observed for LDL cholesterol lower than 1·4 mmol/L (appendix pp 23–24).

Regarding stratification by index case or non-index case, patients who were non-index cases were younger at diagnosis, with lower prevalence of hypertension and diabetes, and lower BMI, although they were more frequently smokers than individuals who were index cases. Untreated LDL cholesterol was approximately 1·55 mmol/L lower in non-index cases versus index cases (p<0·0001; table 2). Prevalence of coronary artery disease or peripheral artery disease were lower among non-index cases than in index cases (all p<0·0001), with no significant difference in stroke (p=0·42; figure 4C; appendix p 45). A similar pattern remained when the results were stratified by both index case or non-index case and sex (appendix p 25). After adjusting for differences including age, sex, cardiovascular risk factors, lipid concentrations, and lipid-lowering medications, non-index cases had lower odds of having cardiovascular disease than index cases, mostly reflected by lower odds of CAD (figure 4D). The Netherlands accounted for most of the non-index case cohort; therefore, this cohort was additionally separated into a non-index case Netherlands cohort and a non-index case cohort excluding the Netherlands (appendix p 46).

Discussion

Registries are a valuable tool to help assess current practices, monitor patients, identify gaps in care (including guideline implementation), and ultimately inform policy.[2] Although familial hypercholesterolaemia registries are available in many countries, aimed at research or to audit

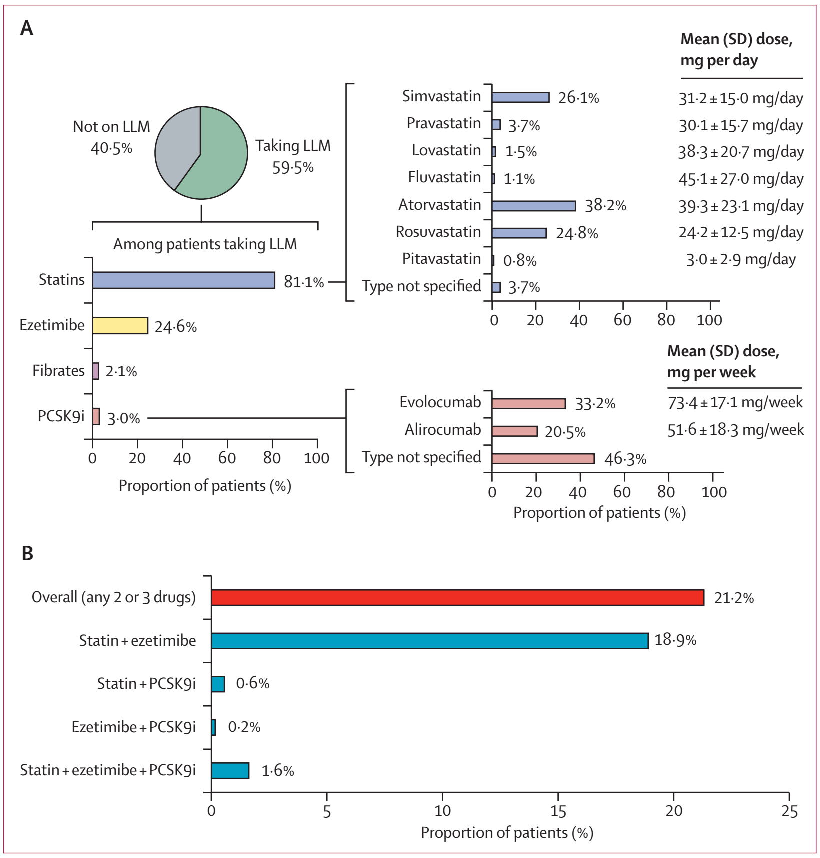

***Figure 5*: Class and type of LLM (A) and combination therapy among participants taking statins, ezetimibe, or PCSK9i (B)**
LLM=lipid-lowering medication. PCSK9i=proprotein convertase subtilisin–kexin type 9 inhibitors.

quality standards, no integrated approach exists globally. Variability in such segregated approaches has complicated efforts to harmonise and integrate information from diverse sources, impeding reliable comparisons across, for instance, different regions and countries to quantify current practices, assess geographical differences in care, and, thereby, inform global public health policy regarding familial hypercholesterolaemia.[5] Through standardisation of nomenclature (FHSC data dictionary), creating a bespoke platform for data entry, and harmonisation, the FHSC attempts to overcome these limitations to provide a global perspective of familial hypercholesterolaemia detection and care.

Our study, the first to report from the FHSC Registry, not only supports and reinforces findings found in local registries, but also provides novel results and expands the findings to include countries that are usually underrepresented in the literature. Our results show that familial hypercholesterolaemia occurs across all WHO regions. Regional variations were observed that could reflect, among other factors, population characteristics, time and method of diagnosis, or differences in detection programmes. Despite familial hypercholesterolaemia being a common condition,[3,11] identification of cases seems to be low. Mean age of diagnosis globally was 43 years in men and 46 years in women, with fewer than half of adult cases diagnosed before 40 years of age and only 2% diagnosed before the age of 18 years. For a genetic condition that, if untreated, leads to lifelong exposure to elevated LDL cholesterol, these data mean that diagnoses, and ultimately therapeutic interventions, occur too late. This might reflect, among other factors, a lack of early screening programmes.[12] Detection globally tends to rely on finding an index case, opportunistic screening such as health checks, or investigation of isolated findings of an elevated LDL cholesterol measurement. Where some form of cascade testing (formal or otherwise) identified non-index cases, identification appeared to be made several years earlier than the average for index cases, with presence of fewer cardiovascular risk factors and lower prevalence of cardiovascular disease.

In addition to the acknowledged effect of familial hypercholesterolaemia on cardiovascular risk, patients with familial hypercholesterolaemia are likely to also be harmed by other risk factors, which can contribute to further increase their cardiovascular risk.[13] In this regard, although the overall prevalence of hypertension was found to be 19·2% and of diabetes to be 5·0% in our study population, these varied by region and both were more common with increasing age. These data highlight that, although familial hypercholesterolaemia occurs globally and there are common goals directed at detection and care, behaviour and cultural aspects might need to be considered in guiding regional health policy, accounting among others for the effect of other risk factors on overall cardiovascular risk. Although most familial hypercholesterolaemia cases were detected after the age of 40 years, we observed that the prevalence of hypertension was only 3·5% and of diabetes was 1·1% among individuals younger than 40 years, underscoring the potential opportunities afforded through early diagnosis of familial hypercholesterolaemia. This could facilitate the need for healthy lifestyles early on to reduce risk of developing additional cardiovascular risk factors later in life.

The most common manifestation of cardiovascular disease was coronary artery disease, with many events occurring prematurely. Although we found a graded relationship between LDL cholesterol concentrations and prevalence of coronary artery disease, no similar trend was observed for either peripheral artery disease or stroke. These findings reinforce the opportunity among individuals with premature coronary artery disease to detect an index case as a means to initiate cascade testing.[13,14] This concept is supported by our observation that among patients who were non-index cases, the prevalence of coronary artery disease was about half and premature coronary disease was about a third of that in patients who were index cases; this underscores the importance of early detection, particularly if done systematically as in the Netherlands. In the absence of a graded relationship between LDL cholesterol and vascular diseases other than coronary artery disease, further work is needed to determine how familial hypercholesterolaemia might be part of a differential diagnosis among individuals with peripheral artery disease or stroke. These observations are in agreement with previous reports suggesting that cardiovascular manifestations of familial hypercholesterolaemia are mainly related to coronary artery disease and, to a lesser extent, to peripheral artery disease, whereas the association of familial hypercholesterolaemia with stroke remains more controversial.[3,15–17]

This study highlights sex disparities in familial hypercholesterolaemia. Although women had broadly similar untreated LDL cholesterol and prevalence of cardiovascular risk factors, the prevalence of coronary artery disease was half that observed in men, even though the average age of familial hypercholesterolaemia diagnosis occurred later in women than in men. By contrast, no clear differences in prevalence of stroke or peripheral artery disease were observed. Because clinical criteria for diagnosis usually include a personal history of premature vascular disease,[4,6] cases of familial hypercholesterolaemia in women, based on our findings, would be more reliant on other characteristics such as physical examination findings or absolute LDL cholesterol. Whether the present scoring systems should be refined with sex-specific criteria is a hypothesis worth investigating to avoid sex disparities in case detection. Sex differences were also observed for therapy, with women less likely to receive higher potency lipid-lowering regimens and less likely to achieve LDL cholesterol goals. Perceived concerns in treating women of childbearing potential might be one factor contributing to sex-related and within-women (pre-menopause and post-menopause) differences in use of lipid-lowering medications.

Globally, individuals with familial hypercholesterolaemia are managed mostly by monotherapy with statins (although only about 14% were receiving the highest doses of atorvastatin or rosuvastatin). Combination therapy of statins with ezetimibe or triple therapy with PCSK9i increases the likelihood of LDL cholesterol goal attainment. Most guidelines recommend LDL cholesterol concentrations lower than 1·8 mmol/L for patients with familial hypercholesterolaemia;[18,19] however, in our study, only 2·7% of patients taking lipid-lowering medications at entry in the registry had LDL cholesterol concentrations lower than that value. Goal attainment improved incrementally with the number of therapies used, with our data suggesting that if the gap between guideline recommendations and clinical practice is to be reduced, greater use of combination therapy and, in particular, PCSK9i are likely to be needed. This raises challenges about accessibility and cost, particularly in low-income and middle-income countries.

The cohort from the Netherlands represents a large proportion of cases in this registry. Therefore, we did a sensitivity analysis for the overall cohort excluding the Netherlands, and one for the Netherlands alone. Additionally, the Netherlands cohort results from a large, nationwide, publicly funded, cascade screening programme that ran for about 20 years,[20,21] leading to the identification of many non-index cases. This situation gave us the opportunity to compare this type of programme with the rest of the FHSC cohort, which mostly relies on case finding, opportunistic screening, and limited cascade screening in some cases. Participants from the Netherlands (overall and non-index cases) were, on average, younger, with lower prevalences of cardiovascular risk factors (except smoking, which was probably related to this cohort running since the 1990s) and cardiovascular disease, and had lower untreated LDL cholesterol. These data reinforce the value of wide screening programmes,

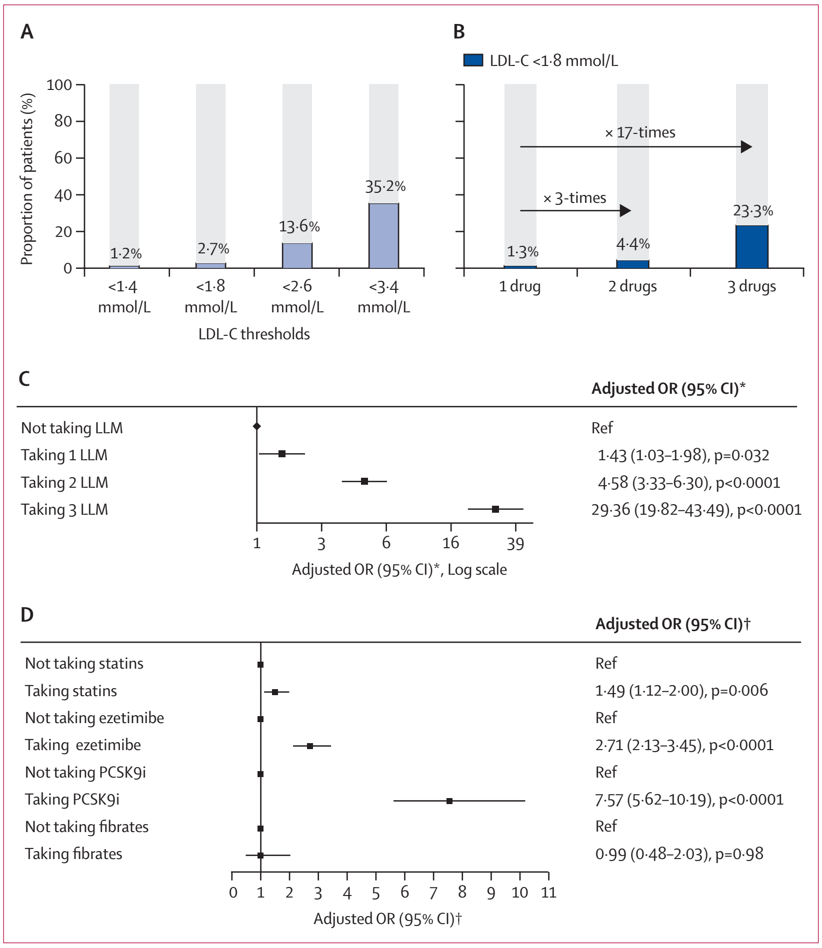

***Figure 6*: Attainment of LDL-C goals among patients on LLMs including statins, ezetimibe, and PCSK9i**
Figure shows the percentage of patients on LLMs (statins, ezetimibe, PCSK9i, or in combination) with an LDL-C lower than different thresholds (A), the percentage of patients on statins, ezetimibe, PCSK9i, or in combination with an LDL-C lower than 1·8 mmol/L on the basis of the number of LLMs taken (B), the odds of attaining an LDL-C lower than 1·8 mmol/L on the basis of the number of LLMs taken including statins, ezetimibe, and PCSK9i (C), and the odds of attaining an LDL-C lower than 1·8 mmol/L on the basis of the type of LLM (D). LDL-C=LDL cholesterol. LLM=lipid-lowering medication. OR=odds ratio. PCSK9i=proprotein convertase subtilisin–kexin type 9 inhibitors. *Adjusted by age and sex. †Each one adjusted by age, sex, and the other types of LLM. Results for the LDL-C goal of <1·4 mmol/L are shown in the appendix (pp 23–24).

supported by appropriate policies and resources, to identify larger numbers of patients with familial hypercholesterolaemia and to do so earlier and when patients might be healthier, which will ultimately affect cardiovascular disease prevention.

The limitations of this study merit consideration. The probability of being included in one of these registers depended on numerous factors. One of the most crucial factors was the local health system and the processes in place to detect and diagnose cases, including the extent to which cascade testing was used. Although the sites participating in the FHSC are major lipid clinics in each of the participating sites, there might be patients with familial hypercholesterolaemia being managed within the same clinics that are not placed onto a local register. Patients with symptomatic vascular disease are more likely to be diagnosed sooner than those without symptoms. Likewise, systematic factors outside of the intrinsic pathological processes might influence the relative likelihood of diagnosis being made on the basis of age and sex. It might well be that, at least in some settings, a patient is more likely to be diagnosed with familial hypercholesterolaemia if, for instance, local or national care pathways ask primary health-care providers to refer patients to specialist clinics, such as the ones recruiting into the FHSC, when LDL cholesterol or total cholesterol concentrations exceed certain thresholds. Data within the FHSC registry come from different sources.[12] Although data sources have broadly similar inclusion and exclusion criteria and standardised information (using a common data dictionary), variability in the data source (eg, different specialist clinics or several diagnostic criteria systems) provides some heterogeneity within the data. The representation of cases from some WHO regions was low. Moving forward, global collaboration can be further enhanced through expansion of the FHSC registry to include data from countries yet to participate, through either provision of individual data or summary data analogous to the French registry. Where genetic testing was not available or accessible, a clinical diagnosis was made; therefore, some patients without a molecular diagnosis, particularly among those with milder phenotypes, might have an alternative condition resembling a familial hypercholesterolaemia phenotype (eg, polygenic hypercholesterolaemia). To limit this from happening, where clinical criteria were applied, only patients with probable or definite familial hypercholesterolaemia were included in the study. Registries are observational by nature, and some variables were not captured in all countries. Although we have statistically adjusted for different variables where appropriate, the presence of potential confounders cannot be fully ruled out for subgroup comparisons. Patients with the most severe phenotypes might have died before they could have been captured in the local registries (potential survival bias). Most local registries are centred in specialist clinics, with some specialisation in lipids, which might imply that gaps in care identified in this study could be more pronounced in general practice or in other non-specialised clinics. Finally, regarding lipid-lowering medications, given that our analyses are done with data from the time of entry in the registry (which, in some cases, is when the patients are first identified with familial hypercholesterolaemia or when they are first referred to a specialist clinic) the treatment might have not yet been intensified. The fact that many patients were included in their respective national or local registries some years ago, before PCSK9i were available, might partly account for the low percentage of patients taking this medication.

In conclusion, this report reveals that familial hypercholesterolaemia is diagnosed late and control of LDL cholesterol concentrations falls far below guideline recommendations, partly because of pharmacological monotherapy-based regimens. Earlier, more systematic detection of familial hypercholesterolaemia and greater use of combination therapy will be required to improve familial hypercholesterolaemia care globally.

Contributors

AJV-V, CATS, KID, TF, GKH, JJPK, PM, FJR, RDS, HSo, GFW, ALC, and KKR contributed to the conception and design of the work. All authors contributed to the acquisition of data, interpretation of data, or both for the work. Each investigator sharing data with the FHSC was responsible for verifying their data before sharing them with the FHSC. AJV-V, CATS, and KID verified the underlying FHSC registry data for the study and did the analysis. AJV-V and KKR drafted the manuscript. All authors critically revised the manuscript and gave final approval for the submission for publication.

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Declaration of interests

CAA-S reports grants from Amgen, during the conduct of the study. FAl reports grants from National Science, Technology and Innovation Plan (MAARIFAH) of Saudi Arabia (08-BIO34-10), during the conduct of the study; and personal fees from Amgen, Amryt Pharma, and Algorithma Pharma, outside the submitted work. RA reports personal fees and non-financial support from Tecnofarma, and personal fees from Novo Nordisk, Abbott, Saval, and Teva, outside the submitted work. KA-R reports personal fees from Sanofi and Abbott, outside the submitted work. NA-S reports personal fees from Sanofi, Amgen, Merck, and AstraZeneca, outside the submitted work. MBa reports grants, personal fees, non-financial support, and other support from Akcea, Amgen, Daiichi Sankyo, Esperion, Freia Pharmaceuticals, Herbapol, Kogen, KRKA, Mylan, Novartis, Novo Nordisk, Polfarmex, Polpharma, Resverlogix, Sanofi–Regeneron, Servier, Teva, Valeant, and Zentiva, during the conduct of the study. SB reports grants from Agence Nationale de la Recherche, Amgen, and Sanofi, during the conduct of the study. CJB reports grants from Amgen, Sanofi, and Alexion, during the conduct of the study; and personal fees from Akcea, Novartis, and Amgen, outside the submitted work. MPB reports personal fees from Amgen and Sanofi, outside the submitted work. MBo reports grants from the Science and Technology Foundation (Portugal) and Akcea, both during the conduct of the study and outside the submitted work. ALC has received honoraria, lecture fees, or research grants from Akcea, Amgen, AstraZeneca, Eli Lilly, Genzyme, Kowa, Mediolanum, Menarini, Merck, Pfizer, Recordati, Sanofi, Sigma Tau, Medco, and Amryt outside the submitted work. PC reports grants and personal fees from Amgen, and personal fees from PTC Therapeutics, Novartis, and AstraZeneca, outside the submitted work. OSD reports grants and personal fees from Amgen and Sanofi, and personal fees from Merck Sharp & Dohme, Daiichi Sankyo, and Novartis, outside the submitted work. KID reports grants from Pfizer, Amgen, Merck Sharp & Dohme, Sanofi–Aventis, Daiichi Sankyo, and Regeneron, during the conduct of the study; and personal fees from Bayer, outside the submitted work. TF reports grants from the Ministry of Health of the Czech Republic, during the conduct of the study; and personal fees from Novartis, Sanofi, and Amgen, outside the submitted work. JG reports grants from the Canadian Institutes of Health Research, during the conduct of the study. AT-H reports personal fees from AstraZeneca, Sanofi, Regeneron, Akcea, Novartis, Silence Therapeutics, and Draupnir Bio, outside the submitted work. MH-S reports grants from the Japanese Ministry of Health, Labour and Welfare, the Japanese Circulation Society, Takeda, Kaneka Medics, and Aegerion; grants and personal fees from Astellas Pharm, Merck Sharp & Dohme, Recordati, and Sanofi; and personal fees from Kowa, Daiichi Sankyo, and Mochida, outside the submitted work. KBH reports grants from Mills and Tine, grants and personal fees from Amgen, and personal fees from Sanofi, outside the submitted work. GKH reports grants from Kowa Research Europe, during the conduct of the study; research grants from the Netherlands Organization for Scientific Research (VIDI), Klinkerpad fonds, and the EU; institutional research support from Aegerion, Amgen, AstraZeneca, Eli Lilly, Genzyme, Ionis, Kowa, Pfizer, Regeneron, Roche, Sanofi, and The Medicines Company; speaker's bureau and consulting fees from Amgen, Aegerion, Sanofi, and Regeneron Pharmaceuticals; and part-time employment by Novo Nordisk. MK reports personal fees from Abbott, Actelion, AstraZeneca, Abdi Ibrahim, Aegerion, Bayer Schering, Menarini, and Sanofi Genzyme; grants and personal fees from Pfizer; and grants from Aegerion, Amyrt Pharma, Amgen, and Sanofi, outside the submitted work. WK reports grants from the Royal College of Physicians of Thailand and the Endocrine Society of Thailand, during the conduct of the study; and grants and other support from Amgen, outside the submitted work. GL reports grants, personal fees, and non-financial support from the Latvian National Research Program Biomedicine for Public Health 2014–17, the Ministry of Education and Science of the Republic of Latvia, and the Latvian Science Council (lzp-2020/1-0151), and personal fees and non-financial support from Amgen, Pfizer, AstraZeneca, Servier, Sanofi, Mylan, Novartis, Merck Sharp & Dohme, KRKA, and Zentiva, during the conduct of the study; personal fees and non-financial support from Bayer, Boehringer Ingelheim, Grindex, Abbott Laboratories, Siemens Laboratories, and Novo Nordisk, and non-financial support from Medtronic, outside the submitted work. EL reports personal fees and non-financial support from the Hellenic Atherosclerosis Society, during the conduct of the study; and personal fees from Amgen, Novartis, Mylan, and Servier, outside the submitted work. ARML reports grants from Pfizer, Amgen, Merck Sharp & Dohme, Sanofi–Aventis, Daiichi Sankyo, and Regeneron, during the conduct of the study. ADM reports funding support for genotyping from the Medical Research Council of South Africa. WM reports grants from Siemens Healthineers, AstraZeneca, Bayer Vital, Bestbion, Boehringer Ingelheim, Immundiagnostik, Merck Chemicals, and Olink Proteomics; grants and personal fees from Aegerion Pharmaceuticals, Amgen, Sanofi, Amryt Pharmaceuticals, BASF, Abbott Diagnostics, Numares, Berlin-Chemie, Akzea Therapeutics, and Novartis Pharma; personal fees from Vifor Pharma; and other support from SYNLAB Holding Deutschland, outside the submitted work. HN reports grants from the Malaysian Ministry of Higher Education, FH-10 countries, University of Western Australia–Familial Hypercholesterolaemia Australasian Network–Asian-Pacific Society of Atherosclerosis and Vascular Disease, and BioEazy; and non-financial support from the European Atherosclerosis Society, during the conduct of the study. BGN reports personal fees from AstraZeneca, Sanofi, Regeneron, Akcea, Amgen, Kowa, Denka Seiken, Amarin, Novartis, Novo Nordisk, Esperion, and Silence Therapeutics, outside the submitted work. FJR reports personal fees from Amgen, Sanofi–Aventis, Regeneron, and Novartis, outside the submitted work. KKR reports grants and personal fees from Amgen, Sanofi–Regeneron, Pfizer, Merck Sharp & Dohme, and Daiichi Sankyo; and personal fees from AstraZeneca, The Medicines Company, Kowa, Novartis, Lilly, Algorithm, Boehringer Ingelheim, AbbVie, Silence Therapeutics, Bayer, Esperion, Abbott, New Amsterdam, and Resverlogix, outside the submitted work. ŽR reports personal fees from Sanofi and Novartis, outside the submitted work. RDS reports grants and personal fees from Abbott, Amgen, AstraZeneca, Akcea, Biolab, Esperion, EMS, Kowa, Libbs, GETZ Pharma, Merck Sharp & Dohme, Merck, Novartis, Novo Nordisk, PTC Therapeutics, Pfizer, and Sanofi–Regeneron, outside the submitted work. HSc reports personal fees from Merck Sharp & Dohme, Amgen, Bayer Vital, Boehringer Ingelheim, Daiichi Sankyo, Novartis, Servier, Brahms, Bristol Myers Squibb, Medtronic, Sanofi–Aventis, Synlab, AstraZeneca, Pfizer, and Vifor, outside the submitted work. CATS reports grants from Pfizer, Amgen, Merck Sharp & Dohme, Sanofi-Aventis, Daiichi Sankyo, and Regeneron, during the conduct of the study. ES reports personal fees from Amgen, Sanofi–Regeneron, Esperion, Novartis, and Novo Nordisk, outside the submitted work. AVS reports lecturer honoraria from AstraZeneca, Abbott, KRKA, Teva Pharmaceuticals, Sanofi, Amgen, Servier, Akrichin, and Janssen. MT reports personal fees from Sanofi, outside the submitted work. LT reports personal fees from Abbott, Amgen, Mylan, Sanofi, Novartis, Recordati, Daiichi Sankyo, and Pfizer, outside the submitted work.

BT reports personal fees from Amgen, Kowa, and Merck Serono, outside the submitted work. ADT reports grants from AstraZeneca and Epsilon Health, and grants and personal fees from Elpen, Libytec, and Galenica, outside the submitted work. AJVV reports participation in research grants to the European Atherosclerosis Society–Imperial College London from Pfizer, Amgen, Merck Sharp & Dohme, Sanofi–Aventis, Daiichi Sankyo, and Regeneron, during the conduct of the study; and personal fees for consulting from Bayer and honoraria for lectures from Amgen, Mylan, and Akcea, outside the submitted work. GFW reports grants and personal fees from Amgen, Regeneron, Sanofi, Novartis, and Arrowhead; and personal fees from AstraZeneca, Kowa, and Esperion, outside the submitted work. SY reports personal fees from Kowa, Merck Sharp & Dohme, Skylight Biotec, Hayashibara, and Recordati Rare Diseases Japan, outside the submitted work. All other authors declare no competing interests.

Data sharing

Data collected in the FHSC registry cannot be shared with third parties owing to clauses in data sharing agreements with data suppliers that do not allow this. Data ownership for the data shared with the FHSC registry remains the property of the data suppliers.

Acknowledgments

The EAS FHSC is an academic initiative that has received funding from a Pfizer Independent Grant for Learning & Change 2014 (16157823) and from investigator-initiated research grants to the European Atherosclerosis Society–Imperial College London from Amgen, Merck Sharp & Dohme, Sanofi–Aventis, Daiichi Sankyo, and Regeneron. KKR acknowledges support from the National Institute for Health Research (NIHR) Imperial Biomedical Research Centre, UK. KID acknowledges support from a PhD Studentship from NIHR under the Applied Health Research programme for Northwest London, UK (the views expressed in this publication are those of the authors and not necessarily those of the National Health Service, the NIHR, or the Department of Health). TF was supported by a grant from the Czech Ministry of Health (NU20–02–00261). JG receives support from the Canadian Institutes of Health Research. The Austrian Familial Hypercholesterolaemia registry has been supported by funds from the Austrian Heart Foundation and the Tyrolean Regional Government. The Gulf Familial Hypercholesterolaemia registry was done under the auspices of the Gulf Heart Association.

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